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A PSYCHOSOMATIC STUDY OF PELVIC CONGESTION*

CHARLES H. DUNCAN, M.D., AND HOWARD C. TAYLOR, JR., M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women)

A SYNDROME, characterized by lower abdominal pain and parametrial tenderness without apparent cause, it is a common and perplexing problem to the gynecologist. In spite of its frequency the disorder has no generally used name, nor is there any accepted cause, pathologic lesion, or well-characterized disturbance of function.

That the disorder has long been a matter of importance is shown by the many designations that have been used. Thus there is the old German term "parametritis posterior chronica,"[7, 11] the newer "spastische parametropathie,"[12, 13, 15] and the still more modern "pelipathia vegetativa."[8, 10] The French have experimented with "congestion pelvienne,"[1, 3, 6] "plexalgie hypogastrique,"[4, 17] and "endosympathoses genitales."[14] The English have tried "broad ligament neuritis"[18, 22] and "pelvic sympathetic syndrome."[21]

The syndrome may appear as a mild, passing disorder, scarcely noted by the patient and regarded as of little importance by the gynecologist. In some cases, however, it is of long standing and a serious handicap to the patient, and presents thoroughly characteristic features to the observing physician.

The most frequent symptom of pelvic congestion is lower abdominal pain, located in the suprapubic region or in either or both lower quadrants. Pain is often referred also to the sacral area, and may radiate into the anteromedial aspects of the thighs. It is characteristically a dull, heavy ache, sometimes with a burning component. On this more constant pain may be superimposed a

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sharper stabbing or cramplike pain, of brief duration, usually in response to a jolt or sudden movement. Pain is commonly increased in the premenstrual phase of the cycle, and is often augmented by coitus.

There is in the majority of cases a nonspecific leukorrhea, and not infrequently some slight intermenstrual bleeding, usually postcoital or premenstrual in timing. Associated premenstrual engorgement and pain of the breasts is sufficiently common that this disorder should perhaps be considered a part of the pelvic congestion syndrome.

Physical signs may include any or all of the following: tenderness of the parametrium, "cystic" enlargement of one or both ovaries, diffuse enlargement of the uterine fundus, and congestion, hypertrophy, and hypersecretion of the cervix.

Undue pain is elicited by palpation of the broad ligaments, gentle compression of an ovary, and, most characteristically, the stretching of the uterosacral ligaments resulting from a gentle attempt to lift the uterus forward with a finger high in the posterior fornix. Cutaneous hyperalgesia is common over the lower abdominal wall and in the sacral area. Nodular induration of the breasts, particularly the outer inferior quadrants, is a frequent finding when premenstrual engorgement has been prominent.

This syndrome has been ascribed to an inflammation,[7] to a spastic condition of the uterosacral ligaments,[12, 13, 15] to a hyperalgesia of the pelvic tissues,[4, 17] and to a disturbance in pelvic vascular function.[1, 6] While not denying possible contributory roles for other mechanisms, Taylor[19] has concluded that the preponderance of the evidence points to alterations in local circulation and fluid distribution as a major factor in the disorder.

It has not been possible to attribute pelvic congestion to any single etiological factor, and its development is almost certainly the result of multiple influences. That one significant factor may be the emotional state is suggested by the prominence of emotional disorders in patients with pelvic congestion noted by many of those who have described the syndrome.[4, 6, 7, 11] On the basis of such observations it has been proposed that pelvic congestion be considered one of the "stress diseases," representing a bodily reaction to stressful life experiences.[20]

Lacking, however, are studies which will characterize early conditioning experiences and adult personality traits of patients with pelvic congestion, or explore the relationship of stressful life situations and emotional reactions to the onset of the disorder. A sychosomatic formulation of pelvic congestion is also unsupported by any evidence of correlation between stress, emotional state, and pelvic circulatory changes of a nature which might lead to local congestion, edema, and pain.

The aims of the present study were thus, first, to characterize the exact psychological background of pelvic congestion and, second, to investigate the relationship of alterations in pelvic circulation to life situations and emotions.

Materials

Of the 36 subjects studied, 10 were private patients and 26 from the clinic service. With the clinic patients the desire to study a representative group and

not one selected for the prominence of emotional symptomatology was achieved, but with the private patients a degree of selection undoubtedly occurred. There were, however, no significant differences in the findings in the two groups.

The patients ranged in age from 21 to 54 years, 32 of the 36 being in the third or fourth decade (Fig. 1). Thirty-two were or had been married and 4 were single. The incidence of the more frequent manifestations of pelvic congestion is given in Fig. 1.

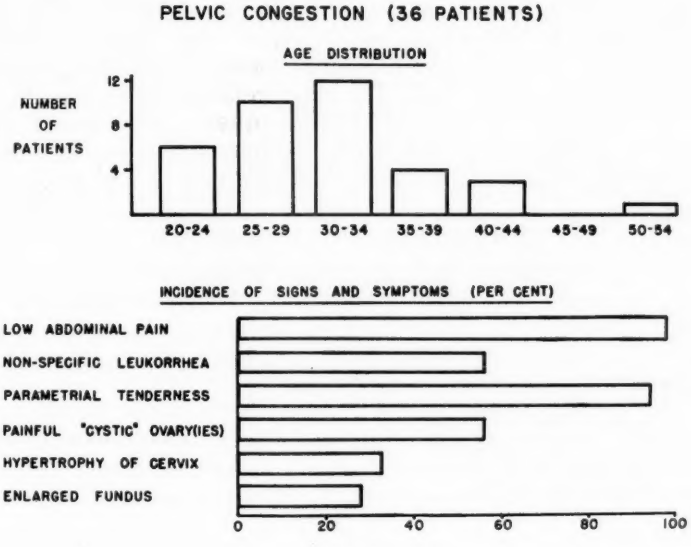

Fig. 1.

Part I: Psychological Background of Pelvic Congestion

The psychiatric evaluation of each patient was based on all contact with her in the course of her office or clinic visits. After initial history and physical examination the one hour allotted for each visit was devoted, except for interval account of symptoms, periodic examination, and minor gynecologic treatment, to a series of face-to-face interviews. In about one-half of the cases a member of the patient's immediate family was also interviewed. The total number of interview hours in each case ranged from 5 to 48, with most patients being seen 10 to 25 times over periods of up to two years.

Childhood Background.—The patients had been, for the most part, members of rather large families, the average number of children being 4.6. There were 3 who had been only children, and the distribution of the other 33 between first, last, and a middle position in the family did not differ significantly from that which would be expected by random selection (Table I).

Despite these unremarkable statistics, inquiry into the patients' early years revealed in most instances a far from tranquil childhood. Twenty-nine expressed the belief that their childhoods had been generally unhappy and abnormal. The more frequent disruptive circumstances in these cases are listed in Table I. The death of 15 of the 72 parents before the patients were 12 years old compares with 5.9 such deaths to be anticipated on the basis of the New York City death rate for individuals age 25 to 44 years during the years 1919 to 1931.

The tabulation in Table I conveys only inadequately the expressed and implied attitudes of the patients toward the lack of affection and security in their early years. Particularly consistent was the belief that they had not received a due share of maternal warmth and care. None of the patients who had lost

their mothers by death had found a satisfactory substitute. Those whose fathers had died apparently did not feel his loss directly, but complained that because of his death the mother had worked or in other ways been prevented from carrying out her responsibilities as a mother. Not one of these 29 patients described even a reasonably satisfactory childhood relationship with her mother.

There remain 7 patients in whom the emotional atmosphere of childhood is less clearly defined. Four of these described unremarkable childhoods except that their mothers played quite minor roles, and each of the 4 had been in her early years much closer to her father than to her mother. The remaining 3 were middle siblings in families of seven, eight, and nine children, and it is possible that there had been undue dilution of maternal warmth and affection.

One possible sequel of the lack of a good relationship with the mother will become apparent upon examination of the subsequent performance and attitudes of the patients in childbearing and child rearing, functions dependent in part on ability to identify with a suitable mother figure.[5]

TABLE I. CHILDHOOD BACKGROUND

	ONLY CHILD	FIRST	MIDDLE	LAST
Position in Family.—				
Actual number	3	9	17	7
(Anticipated)		(8.4)	(16.2)	(8.4)
Family Environment.—				
Unfavorable—29 patients				
Death of parent before patient 12 years old				15
Separation or divorce of parents				6
Psychosis or alcoholism of parent				10
Marked parental discord				13
Rejection of patient in favor of sibling(s)				19
Chronic invalidism of parent				3
Favorable—7 patients				
Mother unimportant—closer to father				4
Middle sibling of 7 or more				3

Adult Attitudes and Behavior.—While it was not always apparent on first contact, the patients were with few exceptions psychologically ill individuals. No attempt has been made to assign to each patient a clinical psychiatric diagnosis, but on the basis of predominant features they would fall into a number of different categories, including conversion hysteria, anxiety hysteria, and obsessive-compulsive neuroses and reactive depression. Several possessed a schizoid personality structure but none was psychotic at the time studied nor gave a history of previous psychotic episode.

Common to all the patients were emotional immaturity and strong dependent needs. All but 5 displayed appreciable anxiety, and all but 10 were subject to periods of depression. Five of the patients admitted to frequent thoughts of suicide and 2 were considered suicidal risks. The frequent occurrence of depression in patients with pelvic congestion has been previously noted, and in 4 of 105 cases reported by Taylor there was a history of attempted suicide.[19]

Inability adequately to express hostility was a prominent trait of 20 of the 36 patients, and anxiety and tension seemed most often to be related to repressed and suppressed hostile feelings. Sixteen patients displayed compulsive behavior or obsessive thinking, and a like number gave a history of motor or sensory disorders or other phenomena strongly suggestive of hysterical conversion symptoms.

Marital Adjustment.—Thirty-two patients were or had at some time been married, and 4 were single. Approximately two-thirds of the married women had married before the age of 20, often to escape from an intolerable home sit-

uation, and in only 6 was the marital relationship reasonably satisfactory. Each of these six had married a sensitive, "motherly" man, and the couple's relationship was an unusually close and mutually dependent one. Two of these couples had no children, and in the other four families the husband had assumed a major share of the care of the children.

Despite the high incidence of expressed dissatisfaction with their marriages only two of the patients had divorced their husbands and two others were separated. This apparent contradiction was in part the result of the insecurity and dependence of the patients which was such that they could not bring themselves to give up the support provided by the husband, inadequate as it might be. Another factor in the many patients with a predominantly masochistic character structure appeared to be the satisfaction of the need to suffer afforded by the marital relationship.

Sexual Behavior and Attitudes.—Particular attention was directed toward attitudes and behavior in the field of sex, and, perhaps because of the nature of the presenting symptoms, very little resistance to such inquiry was encountered. In view of this acceptance it seems certain that the meagerness of the sexual drive and expression elicited is indicative of strong repressive forces rather than conscious withholding of information.

There was an almost complete lack of recall of childhood and adolescent sexual curiosity or experimentation. One patient remembered at age 6 having had gonorrhal vaginitis for which her mother, a nurse, gave her douches on the kitchen table. No other early incidents or circumstances serving to focus attention on the genitals were recalled by any of the patients. Almost half could not recount the circumstances of their first menstrual periods; most thought they had been incompletely prepared for the event, but did not remember their reactions.

Prior to marriage a relative ignorance of sexual matters was common, and several patients described themselves as terribly shocked at the time of marriage by the revelation of its sexual aspects. Only four women gave histories of premarital sexual relations, and three of these only with their future husbands. There were three who had had extramarital sexual relations after marriage, and in two of these it was only after separation from their husbands. Only one of the 36 women might be considered to have been at all sexually promiscuous. There were no instances of overt homosexuality.

TABLE II. SEXUAL AND REPRODUCTIVE PERFORMANCE OF 32 MARRIED PATIENTS

Sexual Performance.—				
Always completely frigid			11	(34%)
Secondary frigidity			19	(60%)
Good marital sexual relationship			2	(6%)
			32	(100%)
Reproductive Performance.—				
Sterile marriages			2	(6%)
Secondary sterility (after 1 to 4 pregnancies)			4	(13%)
No demonstrated infertility (1 to 7 pregnancies			26	(81%)
			32	(100%)
Live birth			62	(67%)
Abortion			31	(33%)
Spontaneous	25	(27%)		
Induced	6	(6%)		
Total number of pregnancies			93	(100%)

Frigidity, though infrequently mentioned as a complaint, generally prevailed at the time the patients were studied (Table II). The 4 single patients had had no sexual experience. Of the 32 who had married, only 2 enjoyed a

good marital sexual relationship. Eleven had always been completely frigid. The remaining 19 had at some time experienced orgasm, or at least found coitus mildly pleasurable, but at the time seen had been frigid for variable periods of time. In most instances the frigidity consisted not only of failure to experience orgasm or to derive any pleasure from coitus, but of active dislike leading to attempts at avoidance whenever possible. Pain experienced in relation to coitus sometimes contributed to this attitude, but it was not the primary factor since in each case frigidity antedated the development of pain on coitus.

In the majority of women with acquired frigidity, it dated from a pregnancy, which would suggest that the frigidity was, at least in part, an expression of the rejection of pregnancy, which was also manifested in other ways.

Reproductive Performance.—The reproductive performance of the 32 married women is summarized in Table II. Two had made sterile marriages and 4, after 1 to 4 pregnancies, failed to become pregnant again despite periods of exposure of one year or longer. The remaining 26 women had from 1 to 7 pregnancies and at no time demonstrated any infertility, perhaps in part because it was masked by the extensive use of contraceptive measures.

The total number of pregnancies for the 32 married women was 93, resulting in 62 live births and 31 abortions, of which 25 were spontaneous and 6 induced. An even higher abortion rate, due to a greater incidence of induced abortions, occurred in the patients with pelvic congestion reported by Taylor; of 145 pregnancies, 80 (55.1 per cent) resulted in live births, 37 (25.5 per cent) in spontaneous abortion and 28 (19.3 per cent) in induced abortion.[19]

Except for an abortion rate that is perhaps high, the reproductive record of the patients does not seem to be unusual. but examination of the attitudes and reactions to the pregnancies is more revealing. A reasonable acceptance of the first pregnancy was achieved by all but one woman. Not that the pregnancies were necessarily planned—actually few of them were—but by the time of delivery only one patient did not have a predominantly positive attitude, or at least one of passive acceptance.

Toward subsequent pregnancies, however, the attitudes were quite different. Of the 26 women who had more than one pregnancy only 8 even approached a willing acceptance of all their pregnancies. Again it is not meant that, in even these 8, the pregnancies were all planned or that the attitudes toward them were not frequently ambivalent. As a matter of fact the ultimate conscious acceptance of pregnancy in these eight was often based on dubious motivation, such as the hope that it would save a disintegrating marriage, or a sense of duty to provide a sibling for an only child. The remaining 18 women maintained completely or predominantly negative attitudes toward one or more of their pregnancies right up to the time of its termination.

Relationship With Children.—That the reluctance to undertake childbearing was in almost every instance acquired rather than primary suggests that these women must have found it a very threatening or burdensome experience. In a few cases labor had been prolonged or delivery difficult, and in others there was disproportion between the patient's concept of her obstetrical difficulties and the known facts. In most instances, however, it was not the pregnancy or the delivery but the subsequent care of the child which was a responsibility to which these immature and dependent women proved unequal.

Eight patients had placed one or more of their children with relatives, foster parents, or in institutions. Twelve women freely expressed resentment at the burden imposed on them by the care of their children. Ambivalent attitudes toward their children existed in others who were not openly rejecting, the negative feelings being expressed in overly restrictive discipline and outbursts of verbal or physical abuse. Underlying hostility could be suspected in

others who were overprotective and overanxious about their children. In no case did the patient derive any real pleasure or satisfaction from her children, and the care of them, at best, was accepted as an unpleasant but necessary duty.

Life Setting at Time of Onset.—The duration of symptoms of pelvic congestion at the time the patients were first seen ranged from one year or less (10 patients) to over ten years (6 patients), with a median duration of three years. In most the onset had been sufficiently abrupt to be readily dated, and particular attention was directed to the life situation and emotional state of the patient at the time symptoms of pelvic congestion first developed. The life setting of the onset of pelvic congestion is summarized in Table III.

TABLE III. LIFE SETTING AT TIME OF ONSET

Pregnancy		19
Unwanted	9	
Extramarital conception	2	
Infant with congenital defect	2	
Postpartum depression	3	
No special features	3	
Family crisis		7
Estrangement or separation from husband	4	
Major problems with children	3	
Conflicts about marriage or sexuality		4
Approaching marriage	2	
Marriage of younger sister	1	
Premarital affair	1	
Loss of supporting figure		4
Death of father	2	
Mother's mastectomy	1	
Separation from parents	1	
No apparent stress		2

The largest group, comprising 19 of the 30 patients who had had pregnancies, dated the onset of illness from pregnancy or the immediate puerperium. According to the patients' accounts and, when they were available, the obstetrical records, there was nothing consistently remarkable about the course of these pregnancies. Two terminated in spontaneous abortion, one in cesarean section performed because of previous pelvic plastic, and the remainder in normal full-term delivery.

There were indications, however, that with the possible exception of three patients, the pregnancy had constituted a major threat. Nine of the pregnancies had been definitely not wanted, and in most of these only fear of complications or persuasion of the family had prevented the patient from seeking an induced abortion. In 2 others extramarital conception led to feelings of guilt about the pregnancy, and in 2 the child had congenital defects. In 3, all first pregnancies, the pregnancy was consciously wanted or accepted but was followed by a prolonged postpartum depression. In the remaining 3 cases there was no indication that the pregnancy constituted any more than the usual stress.

Seven patients developed pelvic congestion in relation to some family crisis. The separation of these patients into two groups is somewhat arbitrary, inasmuch as in 3 of the 4 cases in which estrangement or separation from the husband was the precipitating circumstance, the existence of small children for whom the patient felt inadequate to care was an additional major factor. Similarly, in 2 of the 3 with onset related to development or recognition of major problems with children, chronic marital discord and lack of practical help or emotional support from the husband was a contributing factor.

The precipitating stresses in 4 patients have been loosely grouped as relating to conflicts about marriage or sexuality. Two of these developed pelvic congestion in the setting of indecision about going through with plans for marriage, largely because of doubts as to their adequacy in its sexual aspects. Another developed symptoms when the marriage of a younger sister brought into focus her own unmarried state and the unlikelihood of its ever being changed. The fourth patient dated her pelvic congestion from her first premarital coitus.

In 4 patients pelvic congestion dated from the death or threatened death of, or separation from, an important supporting figure. In 2 patients the onset of pelvic congestion was unrelated to any apparent situational stress.

Less susceptible to tabulation than the stressful situations are the emotional reactions of the patients at the time of onset of pelvic congestion. Those with ability to recall and verbally express their feelings stated that they had been disturbed, describing states of tension, resentment, depression, and anxiety. In others who were less self-analytical, the existence of such feelings in association with the onset of pelvic congestion could be inferred from the manner in which they described contemporary events. Such retrospective assessment of emotional reactions is admittedly subject to distortion, but in many cases confirmatory evidence was supplied by a member of the family. Thus, while some of the stresses in relation to which pelvic congestion developed seem relatively trivial, there was indication in 34 of the 36 patients that they had been emotionally quite significant.

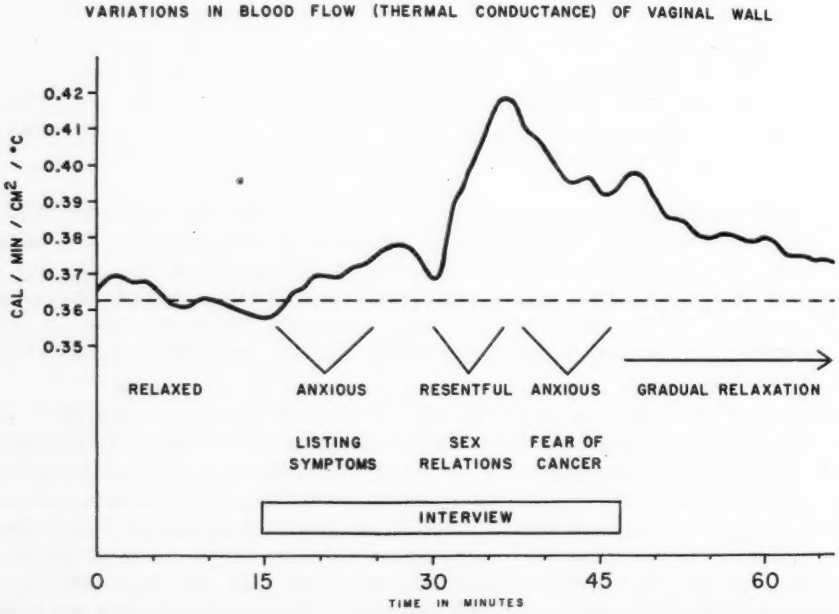

Fig. 2.—At the top is a continuous record of the effective thermal conductance of the vaginal wall, expressed in calories dissipated from the heated element of the instrument per minute per square centimeter vaginal wall in contact with the element per degree centigrade temperature gradient. A rise in the curve represents an increase in effective thermal conductance, and indicates increased blood flow. Below are noted the predominant emotional reactions of the subject during the interview, and the topics of discussion with which these feelings were associated.

Part II: Changes in Pelvic Circulation With Variations in Emotional State

To test the relationship between situations, emotions, and pelvic circulation, ten patients were subjected to one or more experimental studies. Use was made

in the observations of the relationship between the rate of blood flow through a tissue and the effective thermal conductance of the tissue.[2, 16] By means of a modification of the described instruments a continuous record was made of the thermal conductance of the upper lateral vaginal wall. While it is not possible to translate the recorded thermal conductance into units of blood flow, the variations in conductance—other factors remaining constant—reflect the direction and relative magnitude of variations in blood flow.

After a base-line period of approximately 15 minutes during which the patient lay quietly on the examining table or was engaged in neutral conversation, she was led into a discussion of her personal problems. Throughout the interview notes were made both as to the content of the discussion and the patient's emotional reactions. After a period of dealing with topics to which the patient was thought or known to be sensitive, she was again diverted to neutral topics and given reassurance.

At the end of the period of observation the recorded variations in thermal conductance were correlated with topics discussed and the emotional reactions as noted by the interviewer. The results of two representative experiments are illustrated in Figs. 2 and 3.

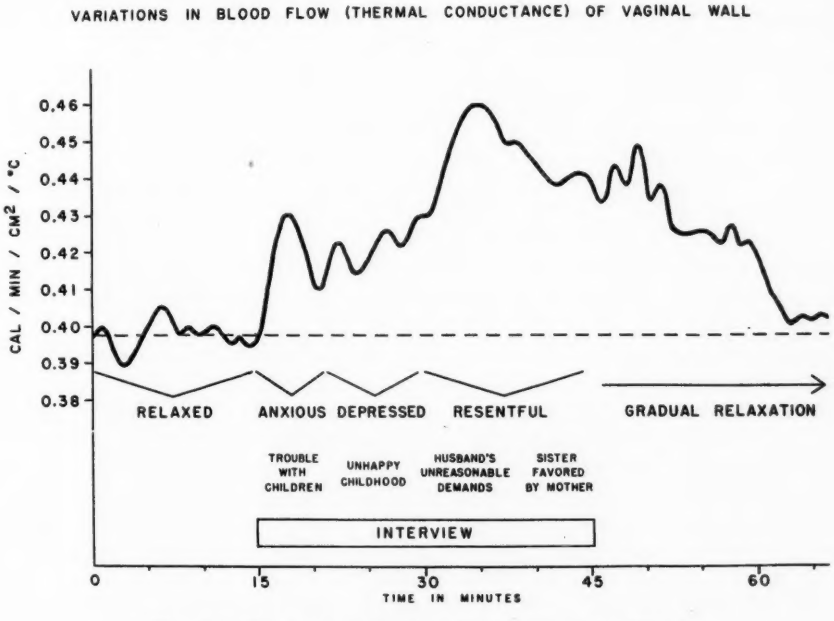

Fig. 3.—The arrangement is the same as in Fig. 2.

In all the experimental interviews vascular changes in the vagina occurred in relation to changes in the emotional state of the subject. In each case the blood flow in the vaginal wall was at relatively low levels during periods of security and relaxation, and increased during the various emotional disturbances incident to the discussion of pertinent problems. The feeling states aroused during the interviews included resentment, anxiety, guilt, and depression. The fact that these feelings rarely occurred singly, but rather in some combination, makes difficult the correlation of increased blood flow with a specific feeling state. In all the interviews, however, as in the two illustrated, the greater hyperemia was associated with resentment, the expression of which was inhibited to some degree by anxiety consequent to any such expression.

Comment

The previously noted prominence of emotional disorders in patients with pelvic congestion[4, 6, 7, 11] is fully confirmed in the present series. The consistency with which the psychiatric studies revealed the patients to be psychologically ill is scarcely compatible with a purely chance association. And while pain may have contributed to the emotional distress displayed, indications in many patients that the emotional disorder antedated the somatic complaints make untenable a view of the psychological illness as exclusively a reaction to the somatic disease. There remains to be considered, then, the alternative conclusion, that emotional factors play a significant etiological role in the clinical syndrome of pelvic congestion.

The concept of pelvic congestion as a bodily reaction to stressful life situations receives support from the high incidence of certain early conditioning experiences and adult character traits shared by the patients. Consistent findings include early experiences which mitigated against identification with a suitable mother figure, emotional immaturity, strong dependent needs, and inadequacy when called upon to function as a woman, either sexually or maternally.

Individual variations as regards other personality traits and emotional reaction patterns are not at all inconsistent with a psychosomatic formulation of pelvic congestion; individuals need not be cast in exactly the same mold in order to display certain similarities in their reactions to stress.

Further indication of an etiological role of life stress and emotions is provided by the observation that in 34 of the 36 patients the onset of pelvic congestion occurred in relation to a stressful life situation. With regard to the nature of the stressful situations and resultant emotional reactions the question of specificity arises. In the individual patient the events were specific, that is, they were events which were particularly meaningful and threatening to her in view of her own past experiences and major areas of emotional conflict. For the group as a whole, however, the picture is less clear, and the question as to why the mechanism of pelvic congestion was the one of choice cannot be answered completely.

The several common psychological features shared by the patients and the general nature of the precipitating stresses do suggest a possible explanation for the choice of the site of the disorder. Thus, the life situations in which pelvic congestion developed were most often ones requiring the patient to function as a woman or serving to raise serious doubts as to her capacity to do so, with pregnancy, marital conflicts, and problems with children leading the list. In a group of women grossly inadequate in the spheres of sexuality and motherhood it is perhaps understandable that the reaction to such stresses should involve the reproductive tract.

When this hypothesis is considered, it is, of course, not possible to say to what extent the frequency of pelvic congestion following pregnancy is attributable to the emotional significance of the event and to what extent it is attributable to the fertile ground for chronic congestion provided by the postpartum pelvic organs.

It should be mentioned that the choice of the mechanism of pelvic congestion was not an exclusive one. Disorders of menstruation, including markedly irregular cycle, hypomenorrhea, and hypermenorrhea, occurred in approximately one-third of the patients. Nor were somatic complaints and evidences of disturbed function limited to the reproductive tract; every patient presented one or more extragenital complaint. Headache, weakness or fatigue, sleep disturbance, and pains of the type commonly attributed to "fibrositis," "myositis," or "muscle tension" were each exhibited by approximately one-half of the patients. Only slightly less common were episodes of nausea and vomiting, urinary

frequency and dysuria, or diarrhea—sometimes superimposed on chronic constipation. Other associated diagnoses in which emotional factors may play a role include essential hypertension, neurodermatitis, alopecia areata, hay fever, and asthma.

Thus, while the evidence points to life stress and emotions as precipitating factors in pelvic congestion, and offers a possible explanation for the choice of the site of the disorder, it is not possible to say to what extent the selection of the particular mechanism of pelvic congestion is determined by other factors.

The exact pathophysiology responsible for the clinical signs and symptoms of pelvic congestion also cannot be stated with any finality. Reference has been made to reasons for implicating vascular phenomena in the genesis of the disorder.[19] Certainly the congestion and edema of pelvic organs—and perhaps the frequency of ovarian cysts and hypertrophied uterine fundus and cervix—can best be understood on this basis. That the lower abdominal pain which is a prominent feature of the syndrome is exclusively the result of these local changes is, however, less evident.

The burning character and unpleasant quality of the pain in some patients with pelvic congestion, its tendency to radiate, and the ease with which it is provoked by peripheral stimulation (e.g., tension on uterosacral ligaments) are characteristics of causalgic pain.[9] The exact mechanism of causalgia is not fully established but all indications are that the phenomenon is due to a maintained disturbance of function somewhere in the afferent pathway by which pain is perceived, the spinal cord being the most likely site of this "physiological inflammation."[9] Although not using the term "causalgia" nor agreeing as to the exact level in the nervous system at which the disturbance exists, both Skajaa[17] and Theobald[21] have recently proposed such a mechanism to account for the pain in the pelvic congestion syndrome.

Decision as to whether the pain is the result of congestion of pelvic structures or whether congestion and pain are parallel results of concomitant vascular and nervous system reactions must await further study. Perhaps both peripheral (vascular congestion and edema) and central disturbances contribute to the pain experienced. In any event alterations in pain sensibility cannot account for the entire syndrome of pelvic congestion and a significant, if not exclusive, role remains for vascular phenomena.

Pelvic hyperemia, as recorded in association with emotional disturbances during the experimental interviews, is one local circulatory alteration which could, if prolonged, lead to congestion and edema. That this is actually the mechanism responsible for the development of pelvic congestion is of course speculative. The existence of a relationship between emotional state and pelvic circulation does, however, make plausible the role of life stress and emotions in the etiology of pelvic congestion which was indicated by the psychiatric data.

One might postulate, then, that the patients reacted to the precipitating life stresses with not only resentment, anxiety, and depression, but also with sustained pelvic hyperemia leading ultimately to the congestion, edema, and pain which characterize the syndrome of pelvic congestion.

Summary and Conclusions

Psychiatric study of 36 patients with pelvic congestion revealed that they had experienced in childhood almost no secure family life after which to pattern their own subsequent existence. Particularly lacking was a satisfactory relationship with a suitable mother or mother substitute with whom the patient could identify. Inability to function adequately as a woman, either sexually or maternally, was displayed by most. Emotional immaturity and strong de-

pendent needs were other common traits. With regard to other personality characteristics there was considerable individual variation, but with few exceptions the patients were psychologically ill.

In 34 of the 36 patients the onset of pelvic congestion was temporally related to a stressful life situation. The stress was in general one which made some particular demands on the patient to function as a woman, the disorder dating from a pregnancy in 19 patients.

In the 10 patients so studied a correlation was noted between emotional changes during an interview and variations in the blood flow of the vaginal wall; increased blood flow occurred during periods of tension, particularly in relation to resentment aroused by discussion of problems with husband and children.

On the basis of these findings it is postulated that along with the emotional disturbance incident to the precipitating stresses the patients also reacted with sustained pelvic hyperemia leading ultimately to congestion, edema, and pain. The patients' major conflictual areas and the nature of the precipitating stresses are perhaps factors in the choice of the reproductive tract as the site of the pathophysiology.

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620 West 168th Street

GROWTH CHARACTERISTICS OF NORMAL AND MALIGNANT CERVICAL EPITHELIUM IN TISSUE CULTURE*

J. G. Moore, M.D., Iowa City, Iowa**

(From the Department of Obstetrics and Gynecology, State University of Iowa)

RECENT widespread interest in the diagnosis of early carcinoma of the cervix has stimulated further efforts in the investigation of this organ. Hinselmann's[1] method of colposcopy, Papanicolaou and Traut's[2] technique of cytologic study, and Gusberg's[3] method of cervical biopsy have all been aimed toward detecting early lesions not obvious to the usual thorough pelvic examination. Much emphasis has been placed on the diagnosis of preinvasive cervical cancer.[4, 5, 6, 7] The malignant potentialities of these intraepithelial lesions have been evaluated by some,[8] but a common rationale of treatment has not been unanimously accepted.[9] Recently, Glatthaar[10, 11] has made efforts to extend our knowledge of questionably malignant lesions of the cervix by a method of tissue culture in combination with phase microscopy. He has attempted to prognosticate the malignant potentialities of preinvasive lesions on the basis of the appearance of growing cells in phase contrast, and on the ability of explanted tissue to grow in vitro.

Many methods have been used in the cultivation of tissue in vitro. The hanging drop method[12] is advantageous in its ease of microscopic observation. The Maximow[13] double coverslip modification of the hanging drop method allows more thorough changes of fluid media without disturbing the tissue. The flask method of Carrel[14] permits a more accurate control of fluid and gaseous exchange, but observation under high power is difficult without special equipment. The roller tube method of Gey[15] employs to advantage simple containers and allows for continuous movement of fluid media over the explanted tissue, but requires a rotor and does not lend itself well to high-power observation. In each method, the explanted tissue is embedded in plasma as the latter is allowed to clot on a glass surface. The explant and clotted plasma are then bathed with a fluid medium which usually consists of embryo extract (chick or bovine), placental cord serum, and a physiological salt solution. At indicated intervals, the fluid and gaseous media are changed, the plasma clot patched with fresh plasma, or the explant together with its new growth subcultured (transferred to a new preparation after subdivision).

Ordinarily, many difficulties present themselves in the maintenance and growth of tissues in vitro.[16] Adult, well-differentiated tissues often lack the ability to grow luxuriantly, whereas rapidly growing tissues present the difficulty of relatively rapid liquefaction of the clotted plasma framework within which the tissue is growing. Problems arising from infection of the explanted tissue have been largely overcome by the use of penicillin and streptomycin. Glatthaar experienced difficulty in growing normal cervical tissue and found

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**Present address, 405 Hilgard Avenue, Los Angeles 24, Calif.

that his rapidly growing malignant tissue liquefied the clot too quickly. It should be stated that these problems are encountered not only in culturing cervical tissue, but with almost all adult mammalian tissue. Evans and Earle[17] introduced a method of utilizing Cellophane as the solid support for migration and growth of cells, a procedure which obviates the problem of liquefaction in tissue culture. More recently they adapted this method to the Maximow double coverslip technique.[18] Simms[19] has developed fluid media which he believes are more adaptable to the growth of epithelial tissue, and White[20] has introduced a fluid medium of simple, reproducible components which, he hopes, may be substituted for the more variable biologic media.

From descriptions of the various methods it is obvious that several techniques and variations might be utilized in culturing cervical tissue. All, however, involve certain fundamental principles which must be recognized. Sterility, careful attention to composition and replacement of fluid and gaseous media, and subculturing at required intervals are paramount in this regard. Mechanically, the methods differ markedly, some affording easier maintenance of the culture, and others permitting more detailed observation. Also, certain variations would seem to lend themselves well to the growth of specific cell types. Consequently, the present investigation is designed not only to study the behavior of normal and malignant cervical tissue in vitro, but to determine methods and conditions best suited for growth of this tissue.

Method and Materials

Attempts were made to culture tissue obtained by biopsy of 28 uterine cervices. Histologic sections were made from one-half of each biopsy and the opposite half was reserved for culture. Eleven of the biopsies were from clinically and histologically benign cervices, and 16 were from tissue which histologically showed epidermoid carcinoma. Intraepithelial carcinoma was generally diagnosed in one cervix, whose tissue was cultured on two different occasions. The women with normal cervices ranged in age from 23 to 42 years, and two were pregnant.

The method of preparing the tissue for culture consisted of the following steps:

1. The patient was instructed to douche with 1:1,000 aqueous Zephiran solution the night before the biopsy.

2. Immediately before the biopsy, the cervix was exposed with a sterile bivalve speculum, thoroughly cleansed with aqueous Zephiran, and carefully rinsed with sterile normal saline solution.

3. Using sharp, sterile Gayler biopsy forceps, a small (5 to 8 mm.), neat biopsy was taken, with every effort made to eliminate excessive crushing and twisting.

4. The tissue was then immersed for 10 minutes in Simms' Z-16 solution* to which 500 units penicillin and 2 mg. streptomycin per cubic centimeter were added. The tissue was then transferred to a second portion of the same solution for an additional ten minutes.

5. Utilizing two No. 7 blades fitted on Bard-Parker handles, the tissue was cut into many (40 to 60) small pieces of less than 1 mm. in any diameter, and again placed in Z-16 (penicillin and streptomycin added) solution for ten minutes. The fluid was pipetted off, fresh Z-16 solution added, and the tissue was considered ready for culture.

6. The cultures were prepared according to the Maximow double coverslip method, or according to the roller tube technique of Gey. Thirty to fifty

*Commercially prepared by Microbiological Associates, Bethesda 14, Md.

separate colonies were prepared from each biopsy. The hanging drop cultures (Maximow) were inverted on suitable racks and incubated at 37.4° C. The roller tube cultures were placed in a rotor apparatus* revolving at the rate of 7 revolutions per hour, and similarly incubated. In most cases commercially prepared, lyophilized chicken plasma,† after being reconstituted, was clotted on the glass surface (Fig. 1) by the addition of a small amount of embryo extract (prepared in our laboratory from 8- to 10-day-old chick embryos, or commercially prepared, lyophilized bovine embryo extract‡ was used). The fluid medium used to bathe the preparations consisted of 4 parts placental cord serum (prepared in our laboratory from placental blood obtained at the time of delivery), 4 parts Simms' solution (with phenol red added as an indicator), and 2 parts embryo extract. One or two drops of the fluid medium were added to the hanging drop preparation, whereas 1½ to 2 c.c. were added to each roller tube preparation. In 7 cases, perforated Cellophane was substituted for the plasma clot in ½ of the hanging drop preparations. In 3 others, autologous serum (the patient's own) instead of placental cord serum was used in the preparation of fluid media.

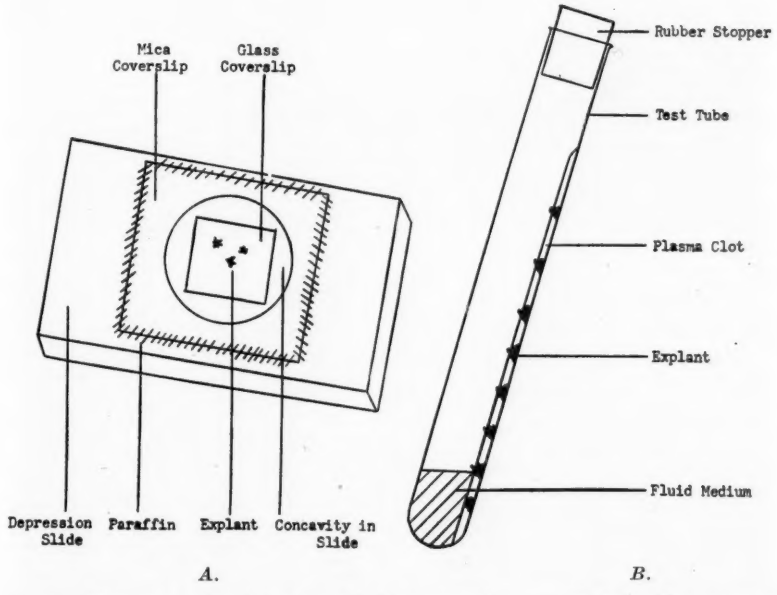


Fig. 1.—*A*, Diagram of culture on double coverslip. *B*, Roller tube preparation.

7. The fluid medium was changed periodically, according to the requirements of the cultures as indicated by the pH and the appearance of the cells; patching with fresh plasma was effected as liquefaction of the clot was observed; and subculturing was carried out as the cells and growth became less vigorous in appearance.

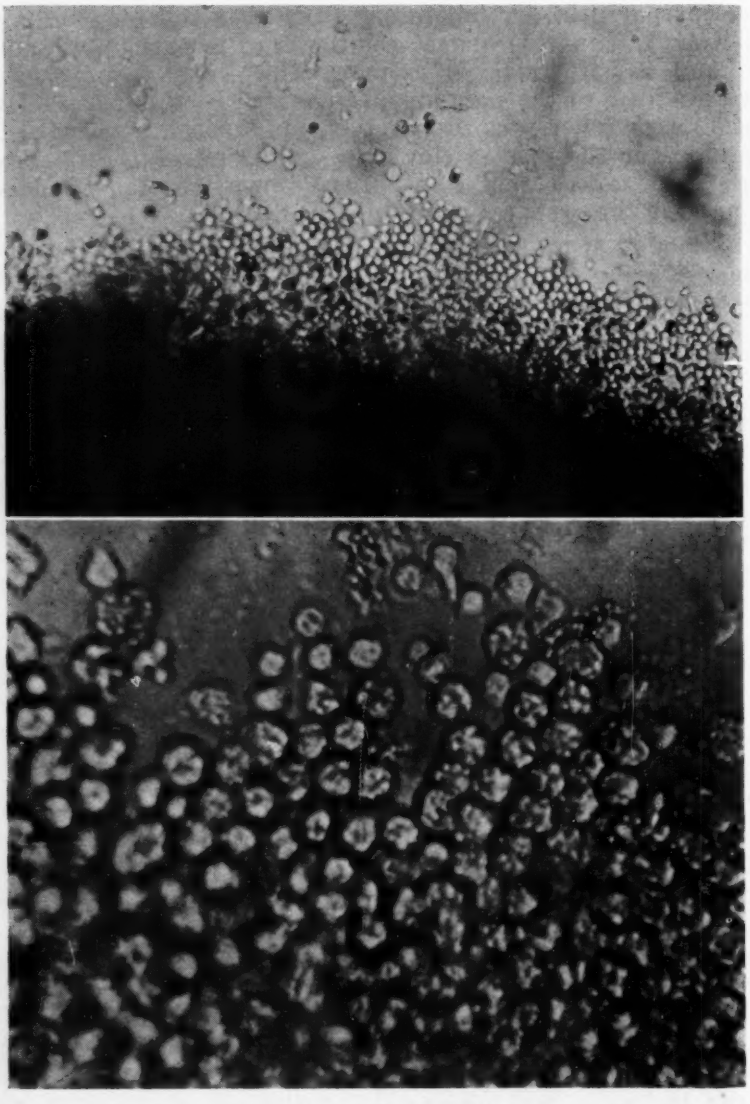
8. Sterile technique was maintained during every stage of the process; observations were made at 1 to 3 day intervals, disturbing the cultures as little as possible, and photomicrographs were obtained to illustrate appropriate points.

*Obtained commercially from Wyble Engineering Development Corp., Silver Springs, Md.
†Difco Laboratories, Detroit 1, Mich.
‡Microbiological Associates, Bethesda 14, Md.

Observations

Cultures of normal cervical tissue proved very difficult to grow by either the coverslip or roller tube method. A limited extension of epithelial cells from the explant took place in 5 out of the 11 normal cervices cultured (45 per cent). Because of the limited extent of the process, it was difficult to discern if it represented true growth on a restricted scale, or whether it was merely a migration or rearrangement of cells originally present in the explant.

A.



B.

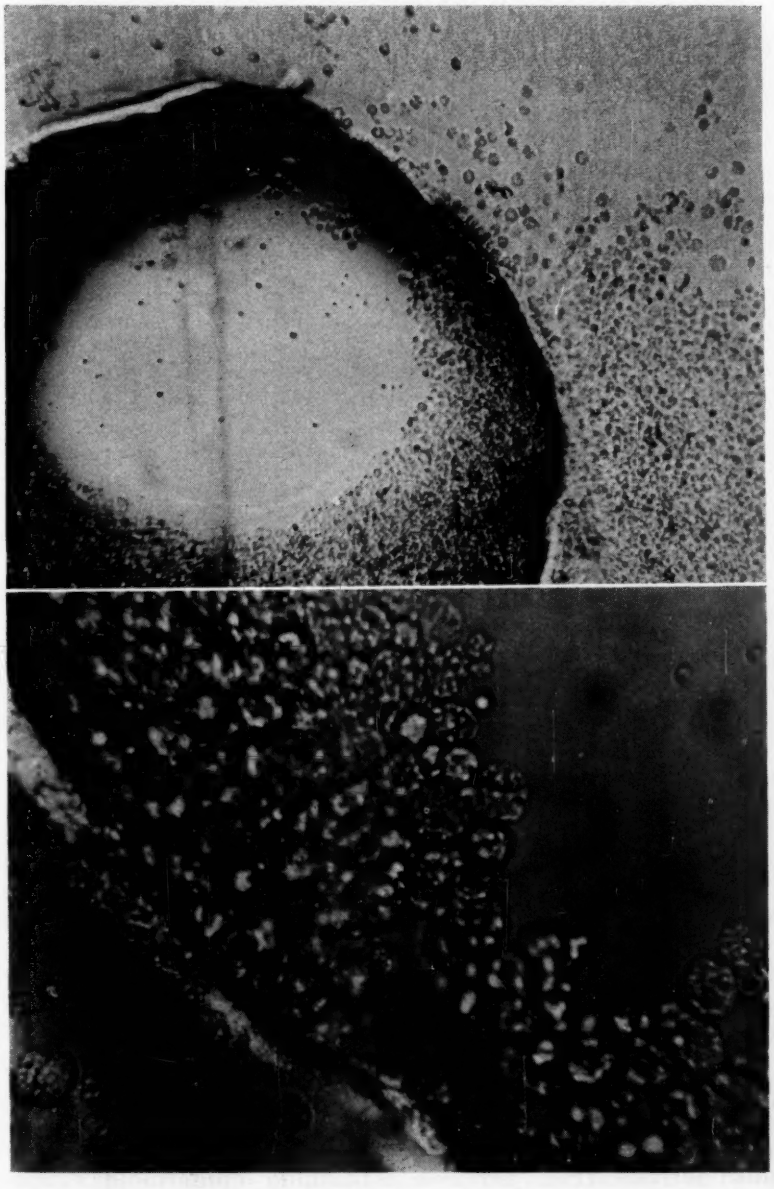
Fig. 2.—Even dispersion of cells from explant of normal cervical epithelium. (*A*, ×200, and *B*, ×600.)

The cells maintained their uniformity (Fig. 2) and took the form of an even mosaic extending from the explanted tissue. This process usually took place over a period of 96 to 120 hours, and the culture then entered a period of relative inactivity during which the cells maintained themselves without

obvious signs of degeneration for as long as 40 to 45 days. Following this period, the cellular elements became granular and vacuolated. Cultures of only one cervix were sufficiently vigorous to survive even one subculture.

Liquefaction of the plasma clot took place to only a limited degree in cultures of normal cervix, although aging of the culture resulted in consider-

A.



B.

Fig. 3.—Cell dispersion from explant of normal cervical epithelium on perforated cellophane. (*A*, ×200, and *B*, ×600.)

able clouding of the plasma. This tendency toward turbidity was present in both the coverslip and roller tube preparations. The perforated Cellophane maintained a relatively clear culture longer than clotted plasma, and, for

purposes of microscopic observation, seemed superior. Also, there was noted a general tendency of the cells to exhibit more extension and dispersion from the explant when perforated Cellophane was used, resulting in a thin even sheet of cells ideal for high-power microscopic observation (Fig. 3).

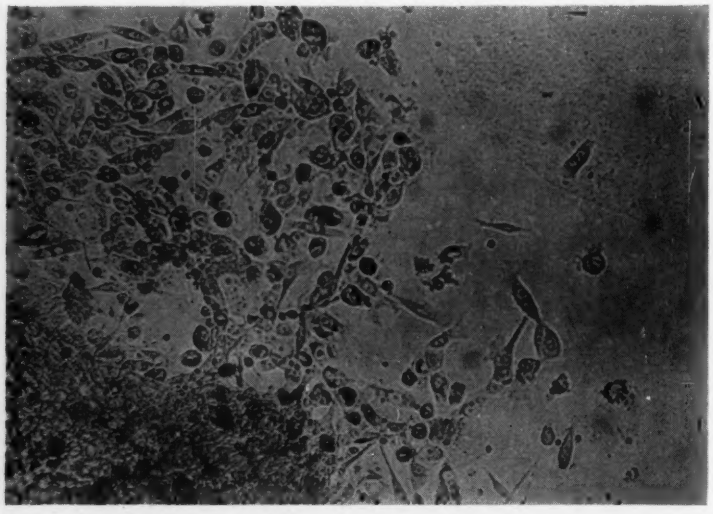


Fig. 4.—Growth of relatively uniform cells from explant of epidermoid carcinoma of the cervix. (×200.)

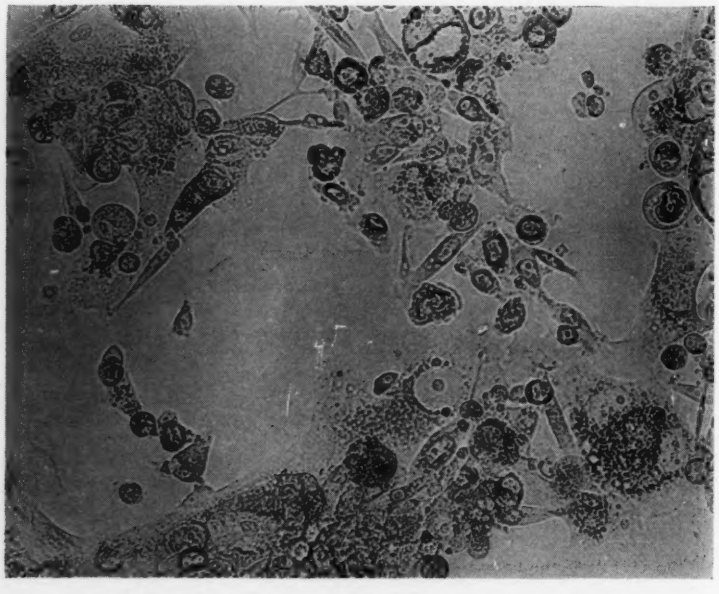


Fig. 5.—Growth of pleomorphic cells from explant of epidermoid carcinoma of the cervix. (×600.)

Explants derived from cervices containing epidermoid carcinoma exhibited a strong tendency to grow vigorously in vitro. The growth occurred early, usually becoming evident microscopically in 24 to 48 hours, and was grossly discernible in 72 hours. Early proliferation was the rule in coverslip cultures but the growth characteristically outstripped its metabolic requirements, and, in spite of frequent replacement of the fluid media and timely

transfers, degeneration became quite evident soon after the early extensive growth. This lability was true also as perforated Cellophane was substituted for the plasma clot. The problem of maintaining a healthy culture and a proper pH was facilitated by the use of roller tubes, and more vigorous and persistent growths were effected by this method. It is of note that 15 (88 per cent) out of 17 carcinomas cultured resulted in significant growth.

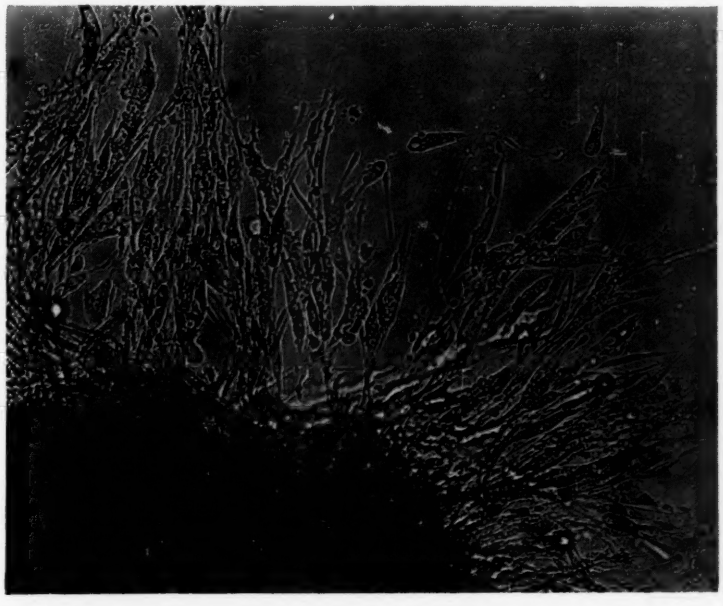


Fig. 6.—Growth of fibrocytes from explant of epidermoid carcinoma of the cervix. (×300.)

It was characteristic that the cell type proliferating from the malignant explants exhibited wide variability. Some cultures showed fairly uniform but actively growing cells (Fig. 4), whereas most displayed marked cellular pleomorphism with significant differences in cell size, shape, and nuclear structure (Fig. 5). Liquefaction of the plasma clot was, in general, much more troublesome with malignant tissue. Patching with fresh plasma, replacement of fluid media, and subculturing were necessary more frequently than with cultures of benign epithelium. Homologous serum supported growth equally well as autologous serum; in fact, it was noted that when the autogenous serum was used, the fibrocytic elements of the growth were somewhat more prominent. Lush growth of fibrocytes sometimes occurred in cultures of malignant epithelial tissue, even though they are not considered part of the neoplastic process in the strict sense of tumor cell types (Fig. 6). This point is emphasized since it was not possible, in this investigation, to initiate active growth of fibrocytes from benign cervical explants.

One case of intraepithelial carcinoma of the cervix, cultured on two different occasions separated by three months, produced significant growth each time. The cell type was uniform and the pattern was fairly well differentiated with the formation of an extensive, regular, mosaic of cells (Fig. 7). This tissue grew as vigorously as any of the malignant tissues cultured. A case of questionable intraepithelial carcinoma (characterized as atypical squamous hyperplasia by some competent observers) was cultured but failed to exhibit any more activity than a limited extension of uniform cells about the edge of the explants (Table I).

TABLE I

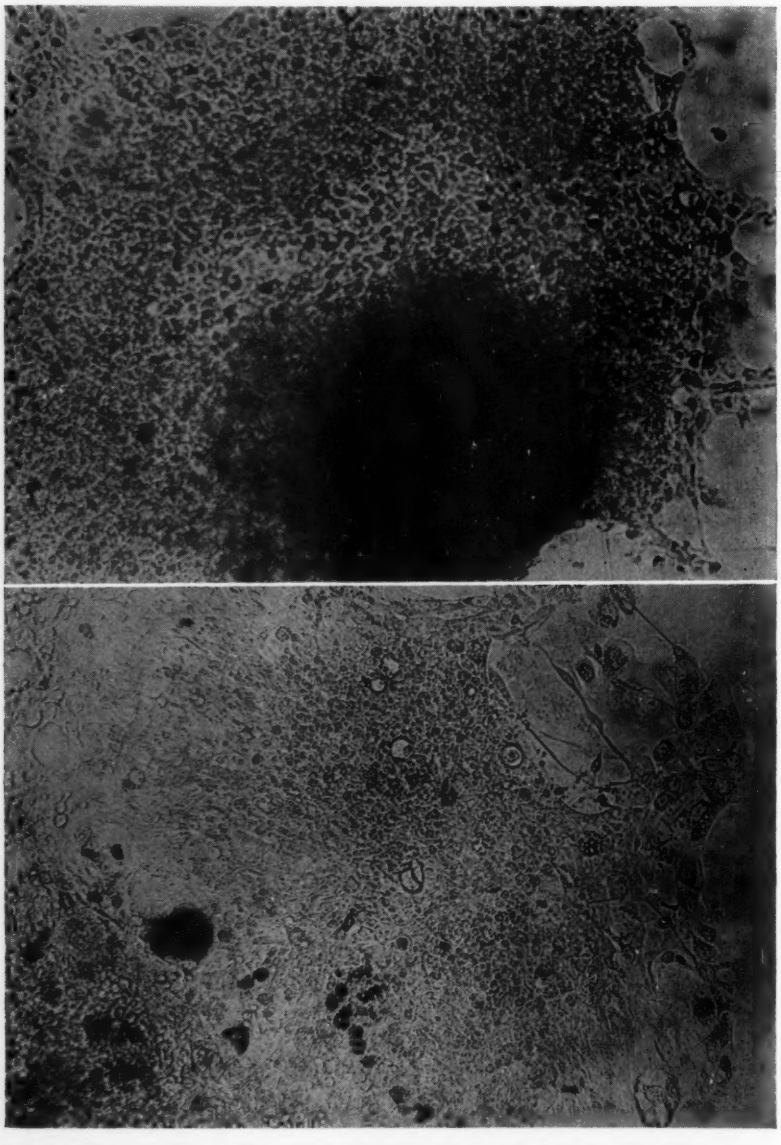
PATIENT	AGE (YEARS)	DIAGNOSIS	METHOD	LIQUEFACTION	GROWTH	COMMENT
M. C.	28	Normal	Plasma clot, coverslip	None	None	Observed 8 days
B. C.	23	Normal	Plasma clot, coverslip	Very little	Limited	Observed 6 days (contaminated)
M. A.	30	Normal	Plasma clot, coverslip	None	None	Observed only 3 days
R. B.	30	Normal	Plasma clot, coverslip	Very little	Slow but fairly persistent extension	Observed 69 days
R. G.	29	Chronic cervicitis	Plasma clot, coverslip	Very little	Slow extension	Observed 42 days
			Perforated Cellophane, coverslip		Moderate extension	Observed 42 days
G. A.	22	Chronic cervicitis	Plasma clot, coverslip	Very little	Slow extension	Observed 42 days
			Perforated Cellophane, coverslip		Moderate extension	Observed 42 days
A. L.	42	Normal	Plasma clot, roller tube	Very little	None	Observed 7 days
H. B.	26	Normal	Plasma clot, roller tube	Very little	None	Observed 5 days
G. S.	33	Normal	Plasma clot, roller tube	Minimal	Slight epithelial extension (questionable)	Observed 25 days
E. B.	19	Normal	Plasma clot, roller tube	Minimal	Moderate epithelial extension	Observed 41 days
S. A.	32	Questionable	Plasma clot, roller tube	Moderate	Limited epithelial and fibrocytic growth	Observed 7 days
B. C.	29	Epidermoid cancer	Plasma clot, coverslip	Very marked	Rapid and extensive growth	Observed 25 days
			Perforated Cellophane, coverslip			
R. W.	27	Carcinoma in situ	Plasma clot, coverslip	Moderate	Fairly rapid but not persistent growth	Observed 8 days
			Perforated Cellophane, coverslip			
G. R.	44	Epidermoid cancer	Plasma clot, coverslip	Moderate	Good growth initially early degeneration	Observed 22 days
			Perforated Cellophane, coverslip			
M. H.	38	Epidermoid cancer	Plasma clot, roller tube	Moderate	Only fibrocytic proliferation	Observed 27 days

E. W.	37	Epidermoid cancer	Plasma clot, roller tube	Very marked	Moderately extensive but not persistent growth	Observed 33 days
J. H.	43	Epidermoid cancer	Plasma clot, roller tube	Moderate	None	Observed 7 days (contaminated)
E. V.	34	Epidermoid cancer	Plasma clot, roller tube	Moderate	Good initial growth	Observed 50 days. Not vigorous enough to survive transfers
D. A.	41	Epidermoid cancer	Plasma clot, roller tube	Marked	Moderately good persistent growth	Observed 46 days
C. K.	40	Epidermoid cancer	Plasma clot, roller tube	Very marked	None	Discontinued after 3 days (contaminated with *Monilia albicans*)
M. S.	64	Epidermoid cancer	Plasma clot, roller tube	Moderate	Good growth with later overgrowth by fibrocytes	Observed 44 days
T. M.	59	Epidermoid cancer	Plasma clot, roller tube	Very marked	Excellent epithelial growth	Observed 27 days
E. W.	53	Epidermoid cancer	Plasma clot, roller tube	Very marked	Good epithelial growth; later, fibrocytic growth	Observed 34 days
E. K.	36	Epidermoid cancer	Plasma clot, roller tube Autologous serum in ½ cultures	Moderate	Very good epithelial growth with some fibrocytic outgrowth	Observed 23 days
M. N.	40	Epidermoid cancer	Plasma clot, roller tube Autologous serum in ½ cultures	Very marked	Good epithelial and fibrocytic growth	Observed 12 days, liquefaction a big problem
D. S.	79	Epidermoid cancer	Plasma clot, roller tube	Moderate	Good epithelial and fibrocytic growth	Observed 17 days
K. W.	27	Carcinoma in situ	Plasma clot, roller tube	Moderate	Very extensive and persistent epithelial growth	Observed 19 days
P. L.	40	Epidermoid cancer	Plasma clot, roller tube Autologous serum in ½ cultures	Moderate	Moderate epithelial and fibrocytic growth	Observed 16 days

Comment

The results observed in this investigation are not new, nor are they necessarily significant in themselves, but they illustrate fairly well the problems involved in culturing cervical tissue, and they indicate possibilities which might be exploited in the future.

A.



B.

Fig. 7.—Outgrowth of sheets of epithelial cells from explant of intraepithelial carcinoma of the cervix. (*A*, ×100 and *B*, ×200.)

First of all, the general outgrowth of cells from the explants, even within the first few days, may be significant from a diagnostic point of view. Certainly, the growth tendency was much more vigorous and extensive with

malignant lesions than with the normal cervical tissue. From this point of view, the coverslip technique might be utilized; the growth differential is evident even within 24 to 96 hours, and it does give rise to a thin sheet of cells which may be readily observed under high-power magnification without special adaptation. The method also lends itself well to phase microscopy which may aid in evaluating the malignant potentialities of questionable entities.

The roller tube technique of tissue culture presents a method which is technically less tedious, and which may be adapted to long-period observations of the metabolism of cervical epithelium. The presence of 1 or 2 c.c. of fluid medium from which growing cells derive their metabolic requirements, and into which they expel their waste products, offers a vehicle for measuring such changes. For such observations to be of maximum significance, it would be desirable that simple, reproducible (synthetic, rather than biologic) media be employed. Such media, as White's, have not been generally recognized as capable of supporting growth over indefinite periods. However, the effects on cell growth of substances added to the media may be observed, and, certainly, the biologic activity of the medium bathing the growing cells may be studied through its effects on experimental animals. The effects of radiation on cells growing in vitro may also be observed.

In order to standardize such investigations and set up conditions of adequate control and reproducibility, it would be desirable not only to employ synthetic media, but to work with an established cell strain of cervical epithelium which could be grown in a constant pattern at a predictable rate. With our present methods, it is not likely that we can establish a strain of normal cervical cells that might be grown consistently and indefinitely; the growth response does not appear to be strong enough. The vigor with which some cultures of epidermoid carcinoma of the cervix grow and survive transfers indicates the likely possibility of establishing cell strains of such tissue. The concept of utilizing an established strain, though desirable from the standpoint of controlled experimentation, might present an additional variable, since it is conceivable that, through repeated cultures, the cells might be sufficiently affected that behavior patterns would no longer be applicable to the original tissue. Earle's[21] experience with the production of malignancy in vitro would serve as a caution in this regard. The applicability of such investigation is most attractive, and indeed may be of practical value as applied to the diagnosis and treatment of questionably malignant lesions of the cervix.

Summary and Conclusions

1. Tissues from 11 normal cervices and from 17 cervical epidermoid carcinomas were cultured in vitro for varying periods of time.

2. The Maximow double coverslip and the roller tube techniques were employed.

3. Normal cervical epithelium was difficult to grow and only a limited extension of cells was noted in 45 per cent of the tissues cultured.

4. Epidermoid carcinoma of the cervix was grown in significant proportions in 15 (88 per cent) of 17 tissues cultured.

5. The coverslip method of tissue culture supported growth of malignant cervical tissue over a relatively brief period of time, but failed to maintain the growth, as metabolic requirements became stringent. The method lent itself well to high-power microscopic observation.

6. Perforated Cellophane, when substituted for clotted plasma in the double coverslip technique, permitted excellent microscopic observation, but did not lend itself well to sustained cultures.

7. The roller tube method allowed more vigorous and extensive growth of the malignant explants, and, in general, cultures were easier to maintain. High-power microscopic observation presented difficulties.

8. Autologous serum in the fluid media supported growth equally well as homologous serum.

9. Biologic investigation of carcinoma of the cervix employing tissue culture is considered.

Addendum: The author wishes to thank Dr. J. H. Randall, Professor and Head of Obstetrics and Gynecology at the University of Iowa, for his generous and inspiring support of this investigation. He would also like to acknowledge his indebtedness to Robert J. Stein, now at the University of Innsbruck, Austria, for initiating him in the methods of tissue culture.

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PLASTIC UNIFICATION OF DOUBLE UTERUS

A Study of 123 Collected and Five Personal Cases

ERWIN O. STRASSMANN, M.D., HOUSTON, TEXAS

(From the Department of Gynecology, Baylor University College of Medicine)

ANY uterus with two separate cavities may be termed a double uterus. Two main groups can be distinguished:

1. The *externally* unified uterus with two chambers formed by a septum. The degrees are: uterus subseptus and uterus septus.

2. The *externally* divided uterus with two cavities formed by two separated muscular bodies or semi-uteri. In this group the degrees are: uterus arcuatus, uterus bicornis unicollis, and uterus bicornis bicollis (didelphys). A double vagina is frequently present in the latter group.

This simple classification of symmetrical duplicities, as suggested by P. Strassmann,[1] is satisfactory for all practical purposes. A more elaborate classification can be found in the literature. The asymmetrical type of uterine malformation concerns mostly the development of rudimentary horns. These cases are not recommended for surgical unification and therefore are omitted in this essay.

The etiology of the various forms of double uterus is based upon incomplete or totally missing fusion of the Müllerian ducts. In many mammals double uteri are the norm. They are physiologically necessary to accommodate numerous fetuses. In the three most highly developed primates and homo sapiens the double uterus is unphysiologic and often accompanied by other abnormalities, especially those of the urinary tract.

Independent of the degree of duplicity the same type of clinical pathology is encountered in many patients. These are, briefly: (1) dysmenorrhea and polymenorrhea, (2) dyspareunia and sterility, (3) habitual abortions, dystocia, malpresentations, postpartum hemorrhages, (4) hematometra, hematosalpinx, endometriosis, and subsequent pelvic inflammatory disease.

I should like to point out that not all women with double uterus have disturbances of these kinds. Some of them may have perfectly normal menstrual functions, normal pregnancies and deliveries, according to various statistics, 25 to 40 per cent. They may even go through life without their abnormalities ever being detected. These patients, however, are the exception rather than the rule. Thanks to the method of hysterosalpingography many more instances of double uteri are found than previously, especially if this test is taken routinely, when nothing else can be blamed for the dysfunction.

It is quite natural that the surgical age created the desire to restore normal function in these instances by surgical means.

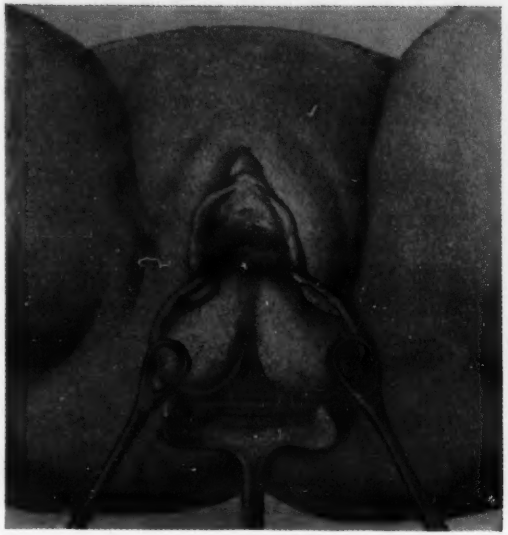

Fig. 1.

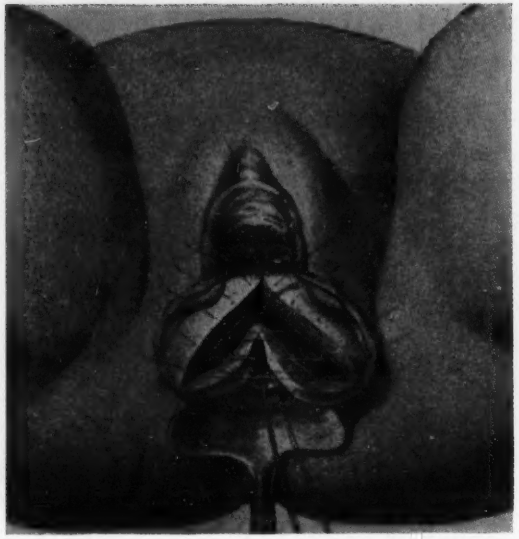

Fig. 2.

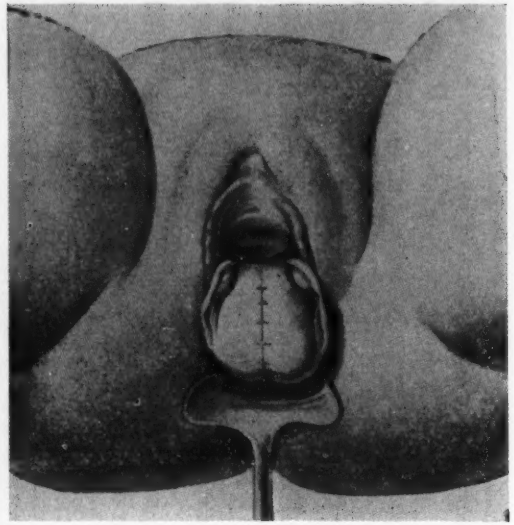

Fig. 3.

Figs. 1-3 are from the first publication of Paul Strassmann.[1]

Fig. 1.—Vaginal approach, first step. Bicornate uterus brought out in front of vulva through anterior colpotomy.
Fig. 2.—Vaginal approach, second step. Semi-uteri opened by transverse incision over saddle into cervix. Sutures placed for unification.
Fig. 3.—Vaginal approach, third step. Two uterine halves united forming one normal-shaped uterus. Note anterior-posterior suture line.

The first step in this direction was the simple removal of the uterine septum done by Ruge and Schroeder in 1882.[2] The patient who had a uterus septus had lost two pregnancies by spontaneous abortion. Within a year after excision of the septum she carried to term and delivered a baby of 3,000 grams without any difficulty.

The removal of the uterine septum was repeated by others but it was obvious that this operation was sufficient only in the externally unified uterus septus, not in the externally divided uterus with two separate corpora.

The idea of plastic unification of a double uterus connecting the two bodies into one was conceived by Paul Strassmann, and executed by him in 1907.[1] He realized that the united normal single uterus provides twice the breeding space as the ununited half uteri.

A few details about his first case which led to the new operation are of interest.

A 27-year-old woman with dyspareunia and dysmenorrhea had experienced 8 pregnancies which all terminated prematurely or as miscarriages. She had undergone 5 curettements. Only one premature baby could be kept alive with considerable effort. She had a uterus bicornis unicollis. The plastic unification was done through the vaginal route which in those days was safer than a laparotomy. Through an anterior colpotomy both uterine bodies were brought out in front of the vulva (Fig. 1) and the adnexa inspected. Then an incision was made across the saddle running transversely from the right cornu to the left. Both uterine cavities were opened and the bridge between them severed until the common cervical canal was reached (Fig. 2). The two opened semi-uteri were adapted to each other by converting the transverse incision into a longitudinal anterior-posterior line. The lateral angles of the actual incision became the center of the suture line and the top of the new fundus. The uterine halves were joined together into one normal pear-shaped single uterus (Fig. 3) by two layers of interrupted catgut. The first layer was stitched through the entire wall on both sides, the second layer superficially through the serosa.

The new uterus was placed back into the pelvis and the anterior uterine wall attached to the bladder peritoneum for anterior fixation and peritonization.

The postoperative course was uneventful. A year and a half after the operation the patient had her first full-term baby. She had five more living children thereafter, altogether six following the operation, all delivered, by the way, per vaginam.

After this encouraging result this operation which in the literature carries Dr. Strassmann's name was performed more and more by him and others. It became a standard operation in European countries, but remained rather unknown on this side of the Atlantic apparently because most papers concerning it were published in German, Italian, French, etc., medical journals.

Dr. Strassmann performed in the course of the years his operation for double uterus on seventeen women. Since I have been practicing in this country I have done 5 cases, which gives us 22 in the family. In his paper "Childbirth Following Strassmann Operation," E. F. Mitteldorf[3] in 1949 compiled a list of the 107 known case reports published so far with all available details.

These 107 cases consist of my father's seventeen cases and 90 cases published by 47 other operators. Five more cases were performed by H. H. Schmid and mentioned by Mitteldorf but not included in his statistics. Eight cases were reported by Ernst Philipp.[6] G. A. Wagner on July 7, 1932, presented a woman who had delivered seven babies spontaneously after he had performed

the operation.[5] Two more cases were done by Felix Rutledge from Houston, Texas, recently and reported to the Texas Association of Obstetricians and Gynecologists.[9]

This gives us a grand total of 128 operations done by 51 different operators, a large enough number to permit an opinion on the merits of this procedure.

Of course, through the years, many more unification operations have been performed which have not been published. For instance, Stoeckel mentioned in 1928 in the Berlin Society of Obstetrics and Gynecology that he had done the operation several times.[3] But these cannot be included in this report, since we do not know either the number or the details.

While my father did 8 of his 17 cases through the vaginal route, most of his followers including myself preferred the simpler approach through the abdomen. The technique of unification is the same. Good illustrations are found in the English translation of the *Textbook on Gynecologic Operations* by Heinrich Martius.[4]

In cases of double vagina and double cervix the laparotomy is preceded by severing the septum of these organs and packing cervix and vagina up to the bifurcation of the uterine bodies.

To the above-mentioned collected 123 cases of unification I should like to add herewith the report of my own five cases.

CASE 1.—Mrs. W. S. W. was 23 years old when I saw her in 1945. Two years before, in 1943, she had lost two pregnancies by spontaneous abortion at 2½ months each. In 1944 a physician suspecting a tumor performed a laparotomy. Fortunately, he realized that he was dealing with a double uterus. He left it untouched and just removed the appendix. Menstruation occurred every 2 weeks with considerable flooding spells. Finally the patient bled three weeks without interruption.

A hysterosalpingogram revealed patent tubes and a uterus bicornis unicollis. The two uterine corpora formed an angle of 145 degrees. The indications for the operation were habitual abortions and menometrorrhagia. On Sept. 9, 1945, the plastic unification of the double uterus was done by laparotomy.

The new normal-shaped uterus was ventrosuspended. The postoperative course was smooth and the patient returned home. There, on Dec. 22, 1947, her physician delivered a living boy of 5 pounds, 10 ounces by elective cesarean section. The baby was in breech presentation.

Not quite two years later, the same physician delivered another boy (6 pounds, 11 ounces) again by cesarean section. Since it was the fourth laparotomy of this patient she was sterilized at this time.

CASE 2.—Mrs. J. B. F., 24 years old, married 4½ years, sought my advice for sterility in 1949. She reported that in 1944, 5 years prior to the consultation, a laparotomy had been done and a cyst removed from the right ovary. The appendix was also removed. Her menstrual history was essentially normal, the husband's sperm satisfactory. An endometrial biopsy indicated ovulation. Hysterosalpingogram revealed a bicornate infantile uterus of the arcuate variety and patency of both tubes (Fig. 4). Since no other factor was found as cause for sterility, a plastic unification was done through the old laparotomy scar on March 17, 1949. The postoperative course was uneventful. The patient became pregnant before her six weeks check-up against our instructions. The pregnancy proceeded undisturbed. The baby was in breech presentation. For this reason a cesarean section was done on Jan. 25, 1950. A normal baby girl of 6 pounds, 12 ounces was obtained. The postoperative course was uneventful.

A hysterogram done in December, 1950, shows a small single uterine cavity and patency of both tubes (Fig. 5).

CASE 3.—Mrs. L. P., 25 years old, had been married for 12 years without ever getting pregnant. She sought advice for sterility in 1949. The menstrual history was essentially negative. In 1940 she had undergone laparotomy for pelvic abscess and appendectomy. A double uterus was found at that time. Hysterosalpingogram revealed a uterus bicornis bicollis with tubes closed apparently at the fimbriated ends (Fig. 6). There was no double vagina.

An intravenous urogram revealed complete absence of the left kidney which was verified by retrograde urography and color secretion test.

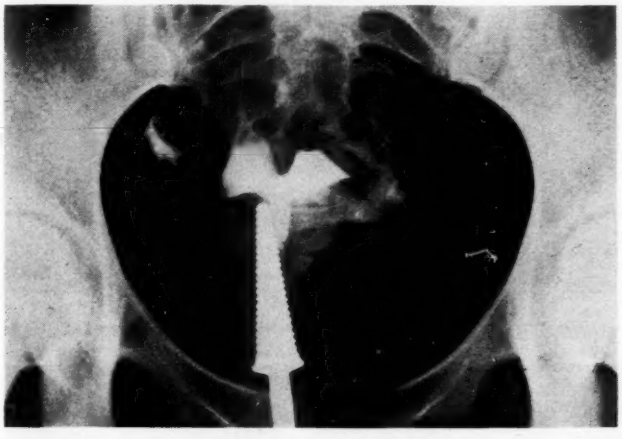

Fig. 4 (Case 2).—Infantile bicornate uterus. Patency of both tubes. Preoperative hysterosalpingogram.

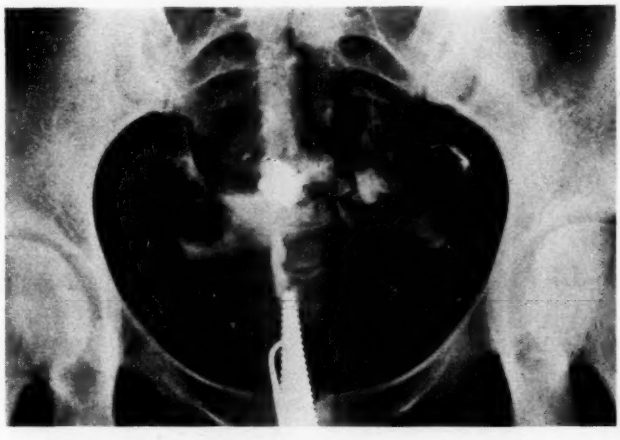

Fig. 5 (Case 2).—Postoperative hysterosalpingogram reveals single cavity. Tubes still patent. Living baby in breech presentation delivered by cesarean section within a year after unification.

On Dec. 10, 1949, the operation was commenced vaginally by dissecting the partition between the two cervices. The abdomen was then opened by excising the old scar. It was found that what we had interpreted as tubes were actually the two uterine bodies forming a straight line (an angle of 180 degrees) and that the tubes were blocked at the isthmus. They could be probed up to the uterosalpingeal junction after severing adhesions around the fimbriated ends.

The plastic unification of the two semi-uteri was done after removal of a strong vesicorectal ligament. In spite of the wide angle between the two uterine bodies there was no tension in the lateral ligaments following the operation. Postoperative course was uneventful. A hysterogram done 8 months after the operation (Fig. 7) shows the new single uterine cavity but no patency of the tubes.

The patient has not become pregnant so far and is not very likely to do so. Her sterility was not caused by the double uterus, but by an obstructing isthmic salpingitis.

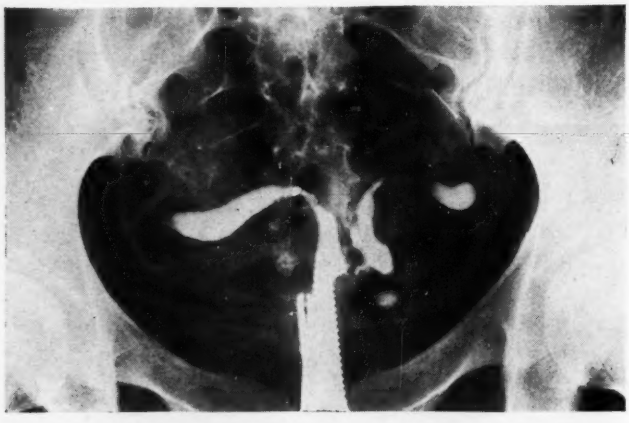

Fig. 6 (Case 3).—Uterus bicornis bicollis. No patency of either tube.

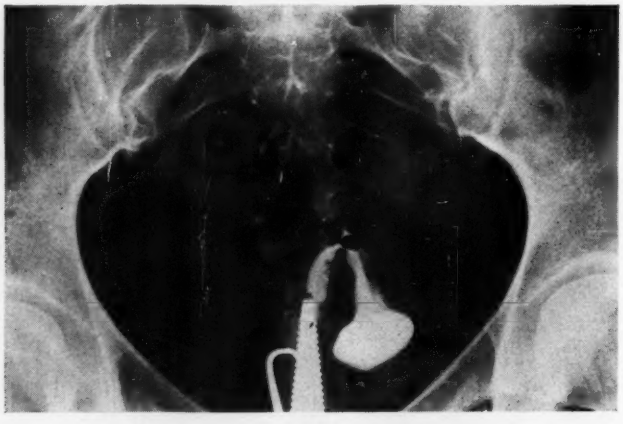

Fig. 7 (Case 3).—Hysterogram following unification of cervices and uteri. Still no patency of tubes. No subsequent pregnancy.

CASE 4.—Mrs. W. H. Sp., 26 years old, came to the office in 1950 on account of sterility and severe dysmenorrhea. She had been married 6½ years. She had seen three physicians previously. Her double uterus had not been detected. The Rubin test revealed tubal patency. The husband's sperm had been satisfactory. The patient had been treated with hormone injections, thyroid tablets, vitamin E, and iron. A hysterosalpingogram on March 14, 1950, revealed a uterus bicornis unicollis and patency of the tubes. The semi-uteri presented a straight line forming an angle of 180 degrees (Fig. 8). The indications for surgery were severe dysmenorrhea and sterility. On April 11, 1950, a laparotomy was done through a Pfannenstiel incision. The double uterus was noted (Fig. 9) and a cyst the size of a walnut containing old blood (endometriosis) was removed from the right ovary. There were other small areas of endometriosis in the cul-de-sac. The two uterine bodies were incised along the median ridges and the cavities opened all the way down into the common cervix.

The semi-uteri were then joined together by converting the original transverse incision into a suture line running sagittally. At the end of the plastic operation the uterus had the shape of a perfectly normal single organ. There was no tension of the lateral ligaments. The uterus was ventrosuspended and the appendix removed. Postoperative recovery was uneventful.

The patient has not become pregnant so far, but her dysmenorrhea is greatly relieved. The chances of pregnancy may be somewhat reduced by endometriosis. A postoperative hysterogram was not taken because of the patient's allergy toward the opaque medium.

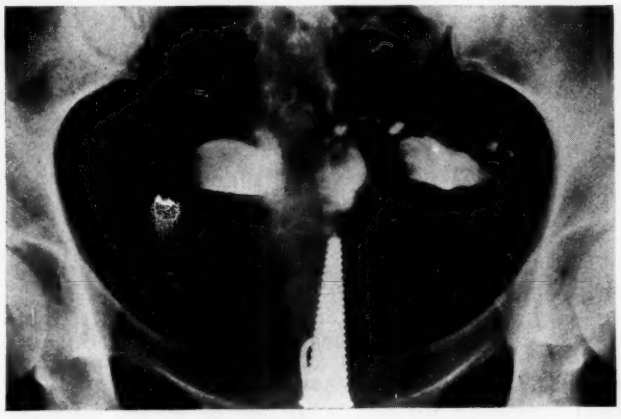

Fig. 8 (Case 4).—Uterus bicornis unicollis. Patency of both tubes. Uterine cavities form an angle of 180 degrees.

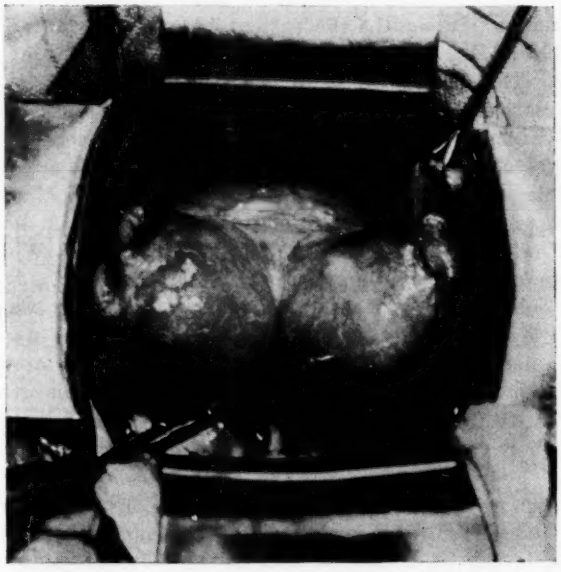

Fig. 9 (Case 4).—Double uterus exposed by laparotomy.

CASE 5.—Mrs. A. E. K., 32 years old and married 8 years, came to the office on account of sterility in 1948. Her menstrual history was essentially normal. Tubal insufflation indicated patency. Endometrial biopsy revealed ovulation. The husband's sperm was satisfactory in quantity and quality. Hysterosalpingogram (Fig. 10) taken on April 11, 1949, showed the so far unknown fact that the patient had a uterus bicornis unicollis which was

tipped to the right. The semi-uteri formed an angle of about 110 degrees. Patency of both tubes was verified. Within a month after the test the patient became pregnant for the first time, but she miscarried spontaneously at 3 months on Aug. 4, 1949.

She became pregnant again in November, 1949, but miscarried a second time after 2 months on Jan. 24, 1950.

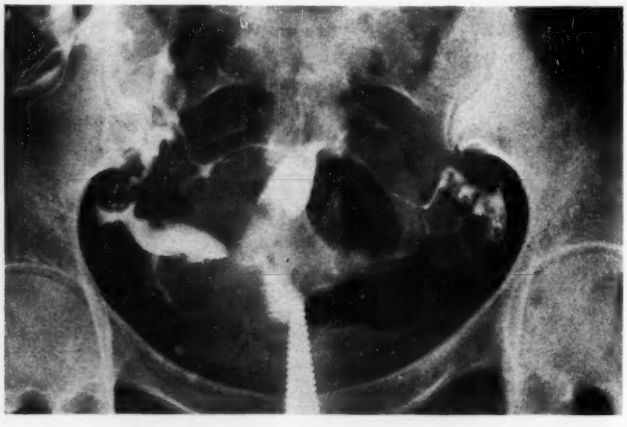

Fig. 10 (Case 5).—Uterus bicornis unicollis with patency of tubes. Habitual abortions preoperatively; vaginal delivery of living infant after unification operation.

Nine years of sterility and two spontaneous abortions following tests and treatments presented a sufficient indication for plastic unification of the double uterus on this now 35-year-old patient. For reason of better healing we waited six months after the miscarriage before performing the operation. This was done on July 29, 1950, through a Pfannenstiel incision. The postoperative course was uneventful. After the recommended waiting period of another six months the patient became pregnant; her last menstruation began on Feb. 19, 1951. Her pregnancy was undisturbed in spite of a lengthy voyage to and through Europe. The expected date of delivery was Nov. 26, 1951. Since the pelvic measurements were satisfactory and the baby in cephalic presentation we did not see any need for elective cesarean section. The patient went spontaneously into labor two weeks after the expected date, on Dec. 9, 1951. The first stage lasted eight hours, the second stage was delayed by right occipitoposterior position. After four hours without noticeable progress and with the fetal heart missing every third beat we felt the baby should be delivered. The fetal head was not quite in midpelvis. While some time elapsed before everything was ready for cesarean section the fetal head advanced to below midpelvis and vaginal delivery by forceps rotation and extraction was performed without undue difficulties. A living healthy girl of 7 pounds, 15½ ounces was obtained. The cord was tight around the neck twice which may account for the circulatory irregularities.

Summarizing my own 5 cases of plastic unification of double uterus, three were done for sterility, two for habitual abortion. Dysmenorrhea and metromenorrhagia were additional indications in 2 cases. Four full-term pregnancies have occurred in 3 patients after the operation. Four living babies have been obtained, three by cesarean section, two of them in breech presentation (one by forceps delivery). In two patients pregnancies have not yet occurred. In one of these the chances are practically nil because of isthmic salpingitis, in the other reduced because of endometriosis.*

Indications and Contraindications

The presence of a double uterus per se is not an indication for plastic unification. This has been stressed by the originator of the operation as well as by most of the operators who published their experience with this method.

*Since the submission of this paper, the author has performed his sixth plastic unification (March 3, 1952). The 29-year-old patient had a history of two spontaneous abortions and was unable to conceive subsequently. A uterus bicornis unicollis was found. The recovery was uneventful.

The main indication is to help those women to become mothers who are prevented from doing so by their malformations. To this group belong patients with habitual abortions and those with sterility. It is the opinion of some that patients with double uterus have no higher percentage of sterility than those with a normal single uterus. That may be primarily true. But it is a fact that in many cases of double uterus hematometra and hematosalpinx develop, and subsequent salpingitis and pelvic inflammation or endometriosis leading to sterility.

Philipp[6] in a recent report on 50 patients with uterine duplicities found 21 of them afflicted with salpingitis. Nine of these women were primarily sterile, while the other 12 were secondarily sterile as a result of tubal inflammation. In order to prevent secondary sterility Philipp recommends not to wait too long with plastic unification which he performed in eight of his cases.

The second indication for this operation is severe menstrual disorders. To this group belong patients with severe dysmenorrhea and patients with menometrorrhagia who do not respond to conservative treatment.

Hysterectomy or removal of one semi-uterus is an unnecessary and mutilating operation, especially in younger women. Only the removal of a rudimentary horn may be justifiable in cases of hematometra or pregnancy with potential rupture. In patients with symmetrical malformation the unification restores the form and with it the function.

In the above-mentioned reported 128 cases of this operation the indications are known in 84 instances. In some of these more than one indication existed. The actual figures are:

Habitual abortion	36	43%
Dysmenorrhea	33	40%
Menometrorrhagia	22	26%
Sterility	13	16%
Dyspareunia	9	11%
Premature deliveries	3	4%

It may be pointed out here that dyspareunia is usually the result of a vaginal septum rather than of a double uterus; it is therefore by itself no indication for metroplastic surgery.

The medical literature is full of reports concerning the clinical pathology and dysfunctions connected with ununited Müllerian ducts. Every case has to be studied on its own merits. It has to be kept in mind that the unification operation is a constructive procedure which provides a physiologic union that nature forgot to complete. Three rules have to be adhered to before a unification should be decided upon:

1. A hysterosalpingogram should be done to determine the exact size and position of the semi-uteri and those of the cervices in cases of a uterus didelphys. The patency of at least one tube should be assured. If bilateral tubal obstruction is encountered, unification for sterility is a useless procedure.

2. An intravenous urogram and in doubtful or abnormal cases retrograde urography and color excretion tests are absolute musts. The frequency of urologic malformations in combination with uterine duplicities has been mentioned above. I observed the absence of one kidney twice, once in a patient prior to the operation, the other time in a patient with a uterus didelphys who had had one semi-uterus amputated by somebody else before I saw her.

3. No unification should be undertaken at the time of an abortion and miscarriage or shortly thereafter. At least 6 months should elapse in order to safeguard good healing and to obtain satisfactory scars.

Postoperative Observations and Results

1. In 128 cases of plastic unification known and published since 1907 there has been only one postoperative death. This occurred in the early days when a pyosalpinx was encountered. This ruptured at operation leading to general peritonitis.

2. There was no maternal death in 83 pregnancies following the operation. Since many of the 128 cases were reported without details or without follow-up the actual figure of 83 postoperative pregnancies does not permit any conclusion concerning the percentage of the women who actually did get pregnant. The known results are encouraging. Seventy-one pregnancies went to term, 61 were delivered per vaginam, 10 by cesarean section. There were 10 miscarriages. In 2 pregnancies the outcome was unknown at the time of publication.

3. There was no case of uterine rupture during pregnancy or delivery. This is remarkable considering the fact that only 10 out of 71 full-term pregnancies were terminated by cesarean section, the remaining 61 babies were delivered per vaginam.

It is the consensus of all operators that the uterine scar following unification can be fully trusted, in contrast to that following cesarean section. The simple explanation is that the scar formation in the puerperal uterus takes place under entirely different biologic conditions.

4. Seventy babies out of 71 full-term deliveries following the operation were born alive. One infant died in utero prior to cesarean delivery in a case of placenta previa.

Functional Results

A high percentage of menstrual disorders in patients with any form of double uterus seems to clear up after the operation. That concerns cases with severe dysmenorrhea as well as those with menometrorrhagia. In none of the reported cases did we find a remark that any of those conditions persisted afterward. In 34 instances complete relief was recorded. In one of my cases where dysmenorrhea existed prior to the operation complete relief was obtained. In two patients with menometrorrhagia this condition subsided postoperatively.

The main indication for surgical unification of double uterus, however, as I see it, is the impossibility of having living children. Here we find the women with habitual abortions and those with sterility in whom all other factors as possible causes have been eliminated.

The individual case reports given have already indicated what the provision of a single normal breeding space can accomplish. Six living children followed the very first plastic unification my father performed in 1907. Four living babies were delivered in 3 of my 5 patients.

In order to put on a percentage basis what we may expect from the operation we have to compare in actual figures the outcome of pregnancies in cases not operated upon with those following the operation.

Philipp[6] whose report of 50 uterine duplicities we mentioned above, recorded 64 pregnancies in 26 of these patients not operated upon.

Sixteen, or 25 per cent, of these pregnancies came to term, 4 with breech presentation and 2 with transverse presentation.

Ten, or 16 per cent, were premature deliveries.

Thirty-eight, or 59 per cent, were abortions or miscarriages.

These figures are fairly representative for all statistical reports of this kind.

In 128 patients, who later underwent plastic unification, the figures are even more outspoken because these patients were selected for surgery by the

various surgeons on account of their disabilities. There were 110 preoperative pregnancies reported in these patients.

Four, or 3.7 per cent, of these pregnancies went to term.

Seventeen, or 15.3 per cent, ended prematurely.

Seventy-seven, or 70 per cent, were miscarriages.

In 12, or 11 per cent, the outcome was unknown or not reported.

So far as pregnancies are concerned which are recorded postoperatively one has to keep in mind that this figure is bound to be incomplete, since many operators reported their cases soon after surgery or did not follow them up long enough to report the full number of pregnancies which may have occurred in the course of the following years. Yet the number and the quality of known postoperative pregnancies are sufficient to evaluate the benefit of the procedure.

A total of 83 pregnancies has been reported (including my own).

Seventy-one, or 85.6 per cent, of these were full-term deliveries.

Ten, or 12 per cent, were miscarriages.

Two, or 2.4 per cent, were undelivered at the time of report or their outcome unknown.

There was no case of prematurity reported.

If we compare these figures with the ones before the operation in these women, we find that the percentage of full-term babies rose from 4 per cent to 85.6 per cent, while miscarriages dropped from 69 per cent to 12 per cent. Even if we add the pregnancies with unknown outcome to the full-term group on both sides the percentage would rise from 15 per cent preoperatively to 86 per cent postoperatively.

If we compare the postoperative figures with Philipp's unselected cases of uterine duplicities not operated upon, we find that the percentage of full-term pregnancies was 25 per cent in cases of double uterus not operated upon and 85.6 per cent in the postoperative group, while the percentage of miscarriages is 59 per cent in the cases not operated upon and only 12 per cent in those operated upon.

TABLE I. COURSE OF PREGNANCIES, SUMMARY

	FULL-TERM (PER CENT)	PREMATURE (PER CENT)	MISCARRIAGES (PER CENT)	OUTCOME UNKNOWN (PER CENT)
In unselected cases of double uterus (64 pregnancies)	25	16	59	0
In cases selected for surgery before operation (110 pregnancies)	3.7	15.3	70	11
In cases selected for surgery after operation (83 pregnancies)	85.6	0	12	2.4

Summarizing, we may state that with proper indication the plastic unification of double uterus, by providing a breeding space twice the size that was present before, more than quadruples the chances of carrying a pregnancy to term while it reduces the chances of miscarriage to less than one-fourth.

So far as sterility is concerned we are hesitant to evaluate the chances of improvement on a percentage basis. The reason for this is that many of the reported cases were done in the early decades before the Rubin test and hysterosalpingography were used. We therefore cannot tell whether sterility was caused by the double uterus or by tubal obstruction and pelvic inflammation. In our own experience sterility can be relieved by the metroplastic operation when no other cause is found besides the double uterus.

Plastic unification of double uterus has been accepted in European gynecology for many years. It is described and illustrated in the textbooks of Victor Bonney, England,[7] Josef Halban, Vienna,[8] Heinrich Martius, Germany,[4] and others. It deserves a place in the textbooks as well as in the gynecologic practice of this country.

Summary

1. A double uterus occurs in two main forms. If two cavities are created by a septum (uterus septus), simple removal of the septum restores a simple cavity. If two cavities are created by two separate muscular bodies (uterus bicornis or uterus bicornis bicollis) plastic unification is necessary to provide a single uterus with normal breeding space.

2. The operation for this condition was conceived and performed for the first time by Paul Strassmann in 1907 on a woman who had 8 miscarriages and premature deliveries before the operation and 6 full-term living babies by vaginal deliveries after the operation.

3. The technique of the operation which can be done either vaginally or by laparotomy is described and the various steps illustrated.

4. Seventeen cases were performed by P. Strassmann, 106 were published by 49 other gynecologists, mostly in Europe, and 5 were done by the essayist, giving a total of 128 known cases so far, done by 51 operators.

5. The five cases of the essayist are described in detail and illustrated by x-ray pictures and a photograph taken during the operation. They were all done for childlessness, caused either by habitual abortion or sterility. Four full-term pregnancies with living babies have occurred in three of these five women after operation so far.

6. The indications for the plastic unification are habitual abortion, sterility, severe dysmenorrhea, and menometrorrhagia. Between 25 and 40 per cent of women with double uterus have no disturbances and do not need surgery.

7. Hysterosalpingography should be done preoperatively to establish the exact size of the uterine bodies and patency of at least one tube. Intravenous urography is a preoperative must to detect abnormalities in the urinary system, not infrequent in these patients.

8. There was one postoperative death in the early days, giving a mortality of one in 128, or less than 1 per cent.

9. There was no maternal death in 83 pregnancies reported following the operation. In many cases no follow-up concerning postoperative pregnancies was included in the publications.

10. There was no uterine rupture during pregnancy or labor. Sixty-one full-term babies were delivered per vaginam, only 10 by cesarean section.

11. Seventy babies out of 71 were living. One fetus died in utero in a case of placenta previa. There were 10 miscarriages, in 2 cases the outcome of the pregnancy is unknown.

12. The percentage of full-term pregnancies in unselected cases with double uterus is about 25 per cent. In cases selected for operation it rises from 3.7 per cent before to 85.6 per cent after the operation.

13. The percentage of miscarriages is 59 per cent in unselected cases. It drops from 70 per cent in cases selected for surgery to 12 per cent postoperatively.

14. The plastic unification of double uterus by restoring the normal breeding space more than quadruples the chances of a living full-term baby in indicated cases. It relieves dysmenorrhea and menorrhagia caused by this condition.

15. The technically simple unification of a double uterus which completes the arrested natural development has become a standard procedure in Europe. It is described in the leading textbooks of gynecologic operations. It deserves a place in the textbooks and the gynecologic practice of this country.

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MANUAL REMOVAL OF THE PLACENTA

HUGH HALSEY II, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

MANUAL removal of the placenta is an operative procedure in obstetrics which has been feared for many years. Its performance is still fraught with many dangers, but the advent of antimicrobial agents, the ready availability of blood, and proper management of the procedure have diminished these hazards. This survey will illustrate the trend in management which has lowered the morbidity and mortality at the New York Lying-In Hospital and the development of indications for the operation.

Three hundred seventy-seven cases of manual removal of the placenta occurred in 53,645 deliveries here in the years 1932 through 1949. This is an incidence of 0.7 per cent which approximates that reported in other studies.

Complications

A. Definitions.—The principal complications of manual removal are infection and hemorrhage, and their resulting morbidity and mortality. Other hazards such as rupture of the uterus and inversion of the uterus are mentioned, but have never occurred here. In 5 cases, inversion of the uterus was an indication for, rather than a result of, manual removal.

The common basis for determining puerperal morbidity is any rise in temperature to 38° C., or above, in two 24 hour periods after the first 24 hours post partum. In this clinic, additional types of morbidity have been classified which when considered all together give a more sensitive indication of total morbidity. These include one-day fever, any elevation to 38° C. or above during any day after the initial 24 hour postpartum period; low-grade fever, any elevation from 37.5 to 37.9° C. during a total of at least 4 days after the initial 24 hour period. These latter morbid reactions represent a lesser degree of infection and make up a greater proportion of the morbidity in these days of the antimicrobials. These 3 types of morbid reaction will be referred to as total morbidity.

Hemorrhage has been classified as any blood loss totaling 600 c.c. or more in a vaginal delivery. This can be an estimated or an actual measured amount. It has always been difficult to be accurate about blood loss, but the principal error is in underestimation. Certainly, it would be safe to assume that all hemorrhage so described had at least the blood loss estimated.

B. Mortality.—There have been 3 deaths in our series of cases, an incidence of 0.8 per cent. None of these deaths can be actually attributed to the manual removal of the placenta. Two of the deaths can be attributed to the hemorrhage which served as the indication for manual removal. In both cases, delayed replacement of blood resulting in irreversible shock was the apparent cause of preventable death. The third death occurred in a woman who died in the second stage of an overwhelming infection due to *Clostridium welchii*. The manual removal was done immediately post mortem.

C. Morbidity.—During the period of this study, there has been a downward trend in morbidity as well as a shorter period of temperature elevation. The puerperal morbidity after manual removal has consistently averaged about four times as great as the general clinic incidence of puerperal morbidity (Fig. 1 and Table I).

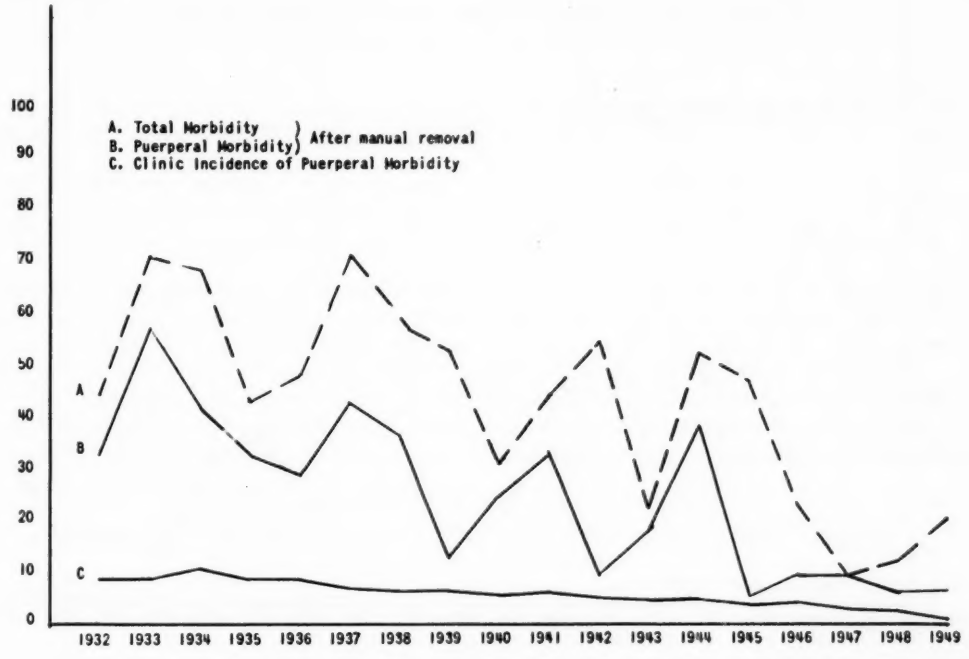

Fig. 1.—Morbidity after manual removal of the placenta.

TABLE I. THE INCIDENCE OF MORBIDITY IN MANUAL REMOVAL OF THE PLACENTA AS COMPARED TO THE CLINIC INCIDENCE

YEAR	MANUAL REMOVAL OF THE PLACENTA		CLINIC
	PUERPERAL MORBIDITY (PER CENT)	TOTAL MORBIDITY (PER CENT)	PUERPERAL MORBIDITY (PER CENT)
1932	33.3	44.4	8.8
1933	57.1	71.4	8.7
1934	42.1	68.4	11.2
1935	33.3	42.8	9.0
1936	29.0	48.4	8.6
1937	42.9	71.4	7.4
1938	36.8	57.9	6.8
1939	13.3	53.3	6.8
1940	25.0	31.3	6.0
1941	33.3	44.4	6.2
1942	10.0	55.0	5.8
1943	18.2	22.7	4.7
1944	38.1	52.4	5.0
1945	5.9	47.1	4.1
1946	10.0	23.3	4.2
1947	10.0	10.0	3.7
1948	6.3	12.5	2.6
1949	6.9	20.7	1.4
Average	25.1	43.1	6.7

D. Hemorrhage.—The incidence of hemorrhage associated with manual removal of the placenta has decreased over the years. The decrease is not marked,

and hemorrhage occurs more frequently where this procedure is performed than in the general clinic incidence (Fig. 2). One hundred twenty-seven cases (33.7 per cent) were associated with a blood loss of 600 c.c. or over. The clinic incidence for hemorrhage in this period was 2.61 per cent.

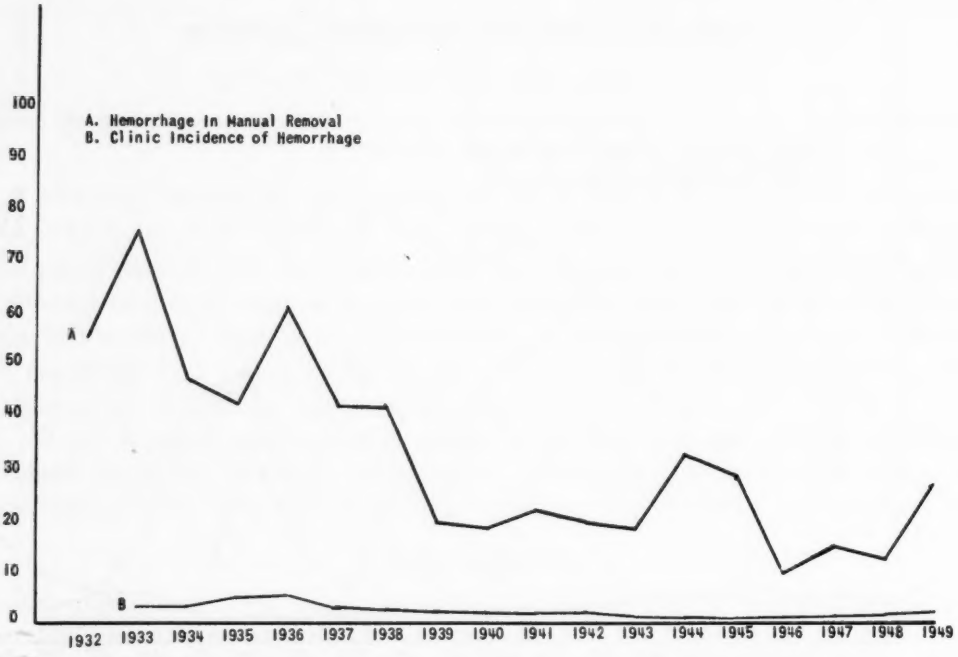

Fig. 2.—Hemorrhage in manual removal of the placenta.

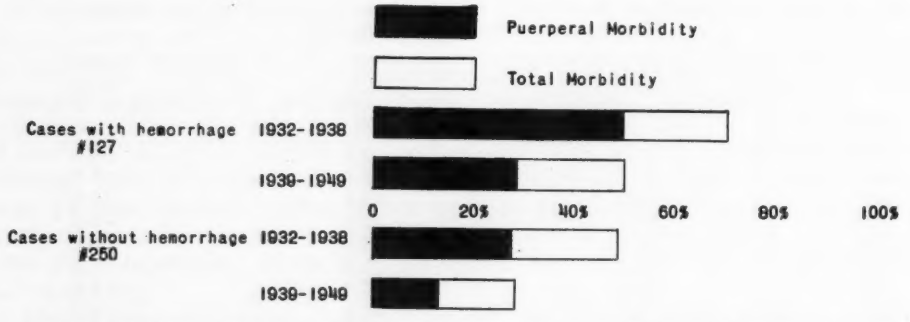

Fig. 3.—Relation of hemorrhage to morbidity in manual removal of the placenta.

The decrease in incidence of hemorrhage associated with manual removal is due to several factors: the more frequent use of oxytocics during and after the third stage, and better management of this stage of labor.

The incidence of hemorrhage on the ward service was 40.1 per cent as compared to 15.3 per cent on the private service, which may reflect more experienced management of the procedure on the latter service.

Increased morbidity in the presence of hemorrhage is a recognized fact and is noted in this series of cases. Since the advent of antimicrobial therapy in 1939, however, the morbidity in these cases has decreased. The greater use of transfusion to replace excessive blood loss is also a factor (Fig. 3).

Indications

A. General.—During the eighteen-year period of this study, two principal indications for manual removal of the placenta have developed, especially on the ward service. These are retention of the placenta for one hour in the absence of bleeding, and excessive bleeding prior to completion of the third stage.

TABLE II. INDICATIONS FOR MANUAL REMOVAL AND MORBIDITY

INDICATION	CASES	PER CENT	MORBIDITY			
			PUERPERAL		TOTAL	
			CASES	PER CENT	CASES	PER CENT
Retention of placenta for 1 hour or more	159	42.2	28	17.3	59	37.1
Excessive bleeding during the third stage	81	21.4	35	44.9	42	51.7
Prophylactic	137	36.4	32	23.4	68	49.6

Excessive bleeding has been arbitrarily designated as 300 c.c. or more. All other manual removals have been classified as prophylactic because they were done incidentally to exploration of the fundus or to facilitate the repair of a cervical or sulcus laceration or simply to shorten the third stage of labor.

An attempt has been made to correlate these indications with the subsequent morbidity. These figures include those from the years prior to the routine use of blood and antimicrobial agents. Once again the importance of blood loss in morbidity is illustrated.

TABLE III. RELATION OF BLOOD LOSS TO MORBIDITY IN PLACENTAS RETAINED ONE HOUR OR MORE

BLOOD LOSS	CASES	PER CENT	MORBIDITY			
			PUERPERAL		TOTAL	
			CASES	PER CENT	CASES	PER CENT
More than 300 c.c.	40	10.6	15	37.5	26	65.0
Less than 300 c.c.	119	31.6	13	10.9	32	26.9

Comparison of the ward and private services shows that morbidity and hemorrhage occur less frequently on the private service, regardless of indication (Tables II, III, and IV).

TABLE IV. COMPARISON OF INDICATIONS, MORBIDITY, AND HEMORRHAGE—PRIVATE COMPARED WITH WARD SERVICES

	INDICATION	CASES	PER CENT	MORBIDITY				HEMORRHAGE	
				PUERPERAL		TOTAL			
				CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Private 98 cases	Prophylactic (to shorten third stage)	66 (59)	67.3 (60.2)	9 (9)	13.6 (15.3)	23 (19)	34.8 (32.2)	5 (3)	7.6 (5.1)
	Retention and bleeding	32	32.7	4	12.5	14	43.8	10	31.3
Ward 279 cases	Prophylactic (to shorten third stage)	71 (33)	25.4 (11.8)	23 (6)	32.4 (18.2)	40 (17)	50.7 (51.5)	15 (3)	21.1 (9.1)
	Retention and bleeding	208	74.6	59	28.3	92	44.2	97	46.6

B. Retention of the Placenta for One Hour.—This was the most common indication for manual removal and was associated with the lowest morbidity. Morbidity was considerably higher in those cases where the blood loss prior to

removal exceeded 300 c.c., an observation which suggests that there should be no delay in initiating the procedure in the presence of bleeding (Table III).

There were three cases in which the placenta was allowed to remain in the uterus for over 5 hours following delivery of the infant. The duration of the third stage was 19, 35, and 50 hours, respectively. All of these patients received antimicrobials prior to and after manual removal was performed, and in no instance was there excessive blood loss or subsequent morbidity. Although these patients suffered no ill effects from the prolonged third stage, it would seem pointless to delay manual removal for so long without good reason. Ninety-five per cent of these patients had the placentas removed within two hours of the first hour of retention.

C. Excessive Bleeding Prior to Completion of the Third Stage.—Excessive bleeding (over 300 c.c.) prior to delivery of the placenta was the least common indication for manual removal, but was associated with the largest morbidity. The period of time during which this bleeding occurred prior to removal of the placenta had little effect on this morbidity.

As an indication for manual removal, excessive bleeding has become even less frequent in recent years; only 20 per cent of the manual removals for this reason have been done since 1941. This is due to the general use of oxytocics in the third stage and to the almost complete elimination of the more traumatic operative procedures which, in most instances, preceded removal for this indication.

D. Prophylactic.—Manual removal as a prophylactic procedure has been performed frequently, and there has been some discussion as to its value as a routine way to manage the third stage.

Prior to 1941, in most instances, prophylactic manual removal was done incidentally to exploration of the uterus following difficult operative procedures such as version and craniotomy, or to facilitate repair of cervical or sulcus lacerations. Since that time, there have been only two cases where it was performed for other than simple retention of the placenta in order to shorten the third stage. In these latter cases, the incidence of morbidity and hemorrhage is still higher than that of the clinic as a whole where more conservative management of the third stage is followed, although it is lower than that following manual removal for other indications (Table IV).

Manual removal of the placenta is performed less frequently on the private service, but, when it is done, it is done most often prophylactically, and with a lower incidence of morbidity and hemorrhage than on the ward service (Table IV). This lower incidence of complications on the private service also applies to manual removals performed for excessive bleeding and retention, and reflects more experienced management of the procedure.

There is a definite trend toward manual removal of the placenta where there is any delay in the completion of the third stage. Many operators prefer to deliver the placenta prior to repair of the episiotomy. Many feel that, if the placenta does not spontaneously separate within 15 to 20 minutes following delivery, spontaneous separation will not occur, and hence they go ahead with manual removal. There are no statistics available to confirm or belie this belief.

Many prophylactic manual removals have been done, but not classified as such, because the whole hand did not enter the uterine cavity. Some operators manage the delivery of the placenta by digital traction on it as soon as it begins to be extruded through the cervix, rather than express it by fundal manipulation.

Tearing the cord in the attempted delivery of the placenta was a complicating factor in 25 cases. These placentas were removed prophylactically in only 4 of these cases, the remainder for retention and excessive bleeding. We have no statistics available as to how frequently this complicating factor occurs,

nor how often the placenta is successfully expressed after the cord is torn free, but it does seem to interfere with completion of the third stage.

Findings at Time of Manual Removal

The findings at time of manual removal were varied. The placenta was found to be totally adherent, partially adherent, or free, in the presence or absence of uterine constriction. An attempt to correlate the findings with the incidence of hemorrhage and the use of oxytocics has been made (Table V).

In the presence of a totally adherent placenta or placenta accreta, there should be no bleeding until removal is attempted. The indication for removal of the totally adherent placenta is thus retention for one hour or more, and the hemorrhage which may occur develops at the time of removal. Attempts to express the adherent placenta by the so-called Credé maneuver, however, will often start bleeding which will necessitate immediate manual removal.

TABLE V. FINDINGS AT MANUAL REMOVAL. RELATION TO HEMORRHAGE AND THE USE OF OXYTOCICS

FINDINGS AT REMOVAL	CASES	PER CENT	HEMORRHAGE		OXYTOCICS IN THIRD STAGE	
			CASES	PER CENT	CASES	PER CENT
Not Incarcerated.—						
Totally adherent	165	43.8	52	31.6		
Partially adherent	91	24.1	49	53.8	158	57.5
Free	19	5.0	6	31.6		
Incarcerated.—						
Totally adherent	21	5.6	3	14.3		
Partially adherent	19	5.0	4	21.1	52	88.1
Free	19	5.0	5	26.3		
No description	43	11.5	11	25.6		

There were no cases of placenta accreta in this series. There were, however, placentas which were densely adherent and were separated with difficulty. The two cases of placenta accreta which occurred in this clinic in the years surveyed were found at cesarean section when difficulty in removing the placenta and hemorrhage required hysterectomy. Placental downgrowth into the uterine musculature was demonstrated histologically. One might postulate that, had the uterus been removed in the cases where the placenta was found to be densely adherent on manual removal, a similar histologic picture would have been found.

Where a partially separated placenta is retained, there is a greater tendency to excessive bleeding which is the indication for the manual removal.

Incarceration of the placenta by some form of uterine constriction is more common when oxytocics are used during the third stage, but the incidence of hemorrhage seems to be definitely decreased.

Evaluation of Possible Factors

A. General.—Any factor which contributes to either the retention of the placenta or excessive bleeding in the third stage must be considered significant, inasmuch as these are the two principal indications for manual removal of the placenta.

B. Age and Race.—On this basis, age and race should have little bearing on the incidence of this procedure. The age distribution curve of the patients in this series follows closely the figures of the United States Birth Registrations which show the greatest number of births between the ages of 20 and 35 years. Ninety-five and two-tenths per cent of the clinic population during the period

of this series were white, and 93.3 per cent of the manual removals were performed on white patients.

C. Gravidity and Parity.—Thirty-five and three-tenths per cent of the patients were primigravidas; 43 per cent were primiparas. This is similar to the national incidence, but somewhat less than the clinic incidence. Ten per cent of the patients were gravida v or more; 5 per cent were para v or more. A higher incidence of manual removal among multiparas may be the result of poorer uterine contractility, especially in the grand multipara group where postpartum hemorrhage due to uterine atony is a fairly common complication.

D. Previous Obstetrical History.—Some previous obstetrical abnormality was recorded in the history of two-thirds of the multigravidas (Table VI).

The most common obstetrical complication was abortion. One might postulate that postabortal curettage might damage the endometrial lining of the uterus so that subsequent implantations would penetrate more readily into the musculature, although there are no data as to how many of these patients had operative completion of their abortions.

TABLE VI. PREVIOUS OBSTETRICAL HISTORY, 244 MULTIGRAVIDAS

	CASES	PER CENT
No abnormality	88	36.1
Abortion	81	33.2
Manual removal of placenta	14	5.7
Previous cesarean section	4	1.6
Puerperal infection	12	4.9
Previous stillbirth	12	4.9
Premature labor	9	3.7
Ectopic pregnancy	6	2.5
Miscellaneous	18	7.4

Manual removal of the placenta was the most common complication in previous pregnancies. The incidence is roughly eight times greater than in the series as a whole. A certain number of these previous procedures were done on a prophylactic basis, but even so there is an increased incidence of manual removal in cases where it has been performed before. The same physiological abnormality which led to the initial manual removal may tend to recur.

Previous cesarean section with adherence of the placenta in the region of the uterine scar has been suggested as a factor in manual removal. There were only 4 cases of manual removal in 327 vaginal deliveries following cesarean section in the years of this study, an incidence not significantly higher than that of this series. In none of these cases was the placenta adherent in the region of the scar.

TABLE VII. ANTEPARTUM COURSE

	CASES	PER CENT
Toxemia	38	9.9
Premature rupture of membranes	36	9.5
Bleeding	27	7.1
Medical disease (excluding heart disease) Tuberculosis, diabetes, syphilis, anemia	23	6.1
Rheumatic heart disease	14	3.7
Hydramnios	5	1.3
Previous myomectomy	2	0.5
Congenital abnormality of uterus	2	0.5
Major abdominal operation	2	0.5
Miscellaneous	14	3.7
Normal	225	59.7

E. Antepartum Course.—Abnormalities of the antepartum course appear to be of little significance. The complicating factors in general approximate the clinic incidence (Table VII).

The cases of toxemia were principally mild pre-eclampsia. Eclampsia did not occur in this series.

Most of the antepartum bleeding occurred at term. In the earlier years, this was a manifestation of placenta previa which was treated with the Voorhees bag, version, and breech extraction, and prophylactic removal of the placenta incidental to exploration of the fundus.

F. Duration of Labor.—The duration of labor and its relation to hemorrhage and morbidity are illustrated in Table VIII. Increased morbidity is a recognized sequela of prolonged labor, but the incidence of hemorrhage is practically the same despite the duration of labor.

There are several factors responsible for the greater incidence of manual removal of the placenta following prolonged labor. Eighty per cent of the deliveries were terminated by operative means under general anesthesia, a method which is accompanied by increased bleeding in the third stage. Retention of the placenta may also be an accompaniment of the impaired physiology which was the cause of the prolonged labor.

TABLE VIII. DURATION OF LABOR, RELATION TO HEMORRHAGE AND MORBIDITY

DURATION OF LABOR	CASES	PER CENT	HEMORRHAGE		MORBIDITY			
					PUERPERAL		TOTAL	
			CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Precipitate (under 3 hours)	21	5.6	7	33.3	4	19.1	4	19.1
Average (3-30 hours)	298	79.0	93	31.2	68	22.8	128	42.9
Prolonged (over 30 hours)	58	15.4	24	41.4	23	39.7	37	63.8

G. Type of Delivery.—Operative delivery preceded manual removal of the placenta in 159 cases (42.2 per cent). This incidence of operative delivery is considerably higher than the clinic average over this period which is about 20 per cent. Most of these deliveries were forceps or breech extractions. Craniotomy, cervical incision, and insertion of the bag are also included, but these procedures have been infrequently performed in the past decade (Table IX).

TABLE IX. TYPE OF DELIVERY

	CASES	PER CENT
Spontaneous	218	57.8
Forceps	92	24.4
Breech extraction	35	9.3
Version	24	6.4
Other procedures (craniotomy, bag, etc.)	8	2.1

TABLE X. TYPE OF DELIVERY AND INDICATION FOR MANUAL REMOVAL

INDICATION	SPONTANEOUS DELIVERY		OPERATIVE DELIVERY	
	CASES	PER CENT	CASES	PER CENT
Retention one hour or more	122	55.9	37	23.3
Excessive bleeding	29	13.3	52	32.7
Prophylactic	67	30.8	70	44.0

There is an increase in the incidence of excessive bleeding as the indication for manual removal following operative delivery. The apparent increase in the number of prophylactic manual removals can be attributed to those incidental to exploration of the uterus following a difficult operative procedure (Table X).

All of these patients received general anesthesia during the operative delivery, nitrous oxide-oxygen-ether principally and open drop ether in a few

cases. Excessive bleeding occurs more frequently with general anesthesia, and is a factor in the increased incidence of manual removal following operative delivery.

H. Anesthesia and Sedation.—Bleeding as an indication for manual removal occurs most frequently when general anesthesia is employed. Where conduction anesthesia is used, this indication is uncommon (Table XI).

TABLE XI. ANESTHESIA, RELATION TO TYPE OF DELIVERY AND TO INDICATION FOR MANUAL REMOVAL

	DELIVERY				INDICATION					
	SPONTANEOUS		OPERATIVE		RETENTION		BLEEDING		PROPHYLACTIC	
ANESTHESIA	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
GOE*	38	17.4	130	81.8	40	25.2	45	55.5	86	62.8
GO†	138	63.3	1	0.6	77	48.4	29	35.9	30	21.9
ODE‡	15	6.9	12	7.5	14	8.8	6	7.4	8	5.8
Local	15	6.9	6	3.8	16	10.1	1	1.2	8	5.8
Local + GO (E)	5	2.3	8	5.0	5	3.1	–	–	3	2.2
Saddle Block	–	–	2	1.3	–	–	–	–	2	1.5
Other	1	0.4	–	–	1	0.6	–	–	–	–
None	6	2.8	–	–	6	3.8	–	–	–	–
	218		159		159		81		137	

*GOE, Nitrous oxide-oxygen-ether.
†GO, Nitrous oxide and oxygen.
‡ODE, Open drop ether.

Saddle-block anesthesia has been used only in recent years in this clinic, and only two cases are included in this series, in both of which the placenta was removed prophylactically. It is an opinion of some that there is an increase in uterine tone following saddle block and caudal anesthesia, and that the use of oxytocics in the third stage will greatly increase the incidence of retained placentas.

Sedation does not seem to be a factor in either excessive bleeding or retention of the placenta (Table XII).

TABLE XII. SEDATION, RELATION TO INDICATION FOR MANUAL REMOVAL

	INDICATION					
	RETENTION		BLEEDING		PROPHYLACTIC	
SEDATION	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Basic.—						
Morphine	31	19.5	25	30.9	34	24.8
Demerol	33	20.8	7	8.7	36	26.3
Barbiturate	12	7.5	8	9.8	22	16.1
Rectal ether	10	6.3	9	11.1	11	0.7
Adjuvant.—						
Scopolamine	52	32.7	13	16.0	63	45.9
Scopolamine and barbiturate	21	13.2	6	7.4	20	14.6
None	73	45.9	32	39.5	44	32.1
	159		81		137	

I. Infant.—The sex and weight of the infants delivered in these cases, as well as the infant mortality, are shown in Table XIII.

The incidence of premature infants is significantly higher than in the clinic as a whole. This is due only in small part to the relatively large number of twins in this series. Delivery of the premature infant through an incompletely dilated cervix is a factor in retention of the placenta. Fifty per cent of these manual removals were done for retention.

Fetal mortality is also higher than the clinic average. This figure includes all deadborn and stillborn infants, and neonatal deaths up to the fourteenth day. This high mortality is associated with a large percentage of operative deliveries, 83 per cent, and three-fourths of the deaths occurred in the first ten years of the series.

TABLE XIII. INFANT STATISTICS, SEX, WEIGHT, AND MORTALITY

	CASES	PER CENT	CLINIC INCIDENCE IN PER CENT
Male	188	44.8	50.4
Female	208	55.2	49.6
Premature 1,500–2,499 grams	44	11.4	2.7
Term 2,500–3,999 grams	314	79.3	85.7
Excessive size 4,000+ grams	37	9.3	11.9
Twins	19	5.0	1.6
Mortality	47	11.8	2.9

J. Oxytocics.—The use of oxytocics during and following delivery has become generally accepted in this clinic. The purpose of their use has been to decrease the blood loss associated with delivery. In so far as this objective has been attained, excessive bleeding as an indication for manual removal of the placenta has decreased. On the other hand, the use of oxytocics prior to the completion of the third stage seems to increase the incidence of retention of the placenta. These two effects apparently balance, and it is obvious that a retained placenta in the absence of bleeding is the preferable situation to face.

There has been no set routine in the use of oxytocics following delivery in this clinic. In the first three years of the series, no oxytocics were used until the third stage had been completed, and in this group more than half of the manual removals were performed for excessive bleeding and more than half had a blood loss exceeding 600 c.c. In some instances, no oxytocics were used at all. In recent years, oxytocics have been given after delivery of both infant and placenta, or after the infant only.

An attempt has been made to correlate the various methods of use with the occurrence of hemorrhage and incarceration. In some instances, the number of cases is too small for significant appraisal. In general, however, the figures seem to show that the use of oxytocics decreases the amount of bleeding, but increases the incidence of retention of the placenta (Table XIV).

TABLE XIV. USE OF OXYTOCICS, RELATION TO HEMORRHAGE AND INCARCERATION

METHOD USED	CASES	PER CENT	HEMORRHAGE		INCARCERATION	
			CASES	PER CENT	CASES	PER CENT
No oxytocic	7	1.8	3	47.9	1	14.3
After infant only	18	4.8	3	16.7	3	16.7
After placenta only	119	31.6	49	41.2	5	4.2
After infant and placenta	188	49.9	58	30.9	39	20.7
No description	41	10.8	10	24.4	8	17.0
Before delivery	4	1.1	4	100.0	-	-

Oxytocics given after the infant only is a method which has become popular in recent years. Ergotrate or Pitocin is given intravenously following delivery of the head or anterior shoulder. Professor William Nixon of the University College Hospital, London, England, in a recent visit to this hospital, presented information purporting to show that ergot preparations tend to cause a generalized contraction of the uterus and cervix, while Pitocin tended to affect primarily the corpus, causing peristaltic contractions. Perhaps the use of Pitocin would be preferable, in the light of this information, by decreasing the incidence of hemorrhage without increasing too greatly the incidence of incarceration of the placenta.

There were four cases of manual removal of the placenta following intravenous Pitocin stimulation of labor. In all these cases, hemorrhage occurred and was the indication for the procedure. Incarceration of the placenta was not described. Three of these patients received 30, 87, and 237 minims of Pitocin, respectively; one received only 2.4 minims. The large amount of Pitocin used in three of the cases is indication of a refractory uterus, a condition which evidently persisted following delivery.

K. Postpartum Events.—Only two patients in this series required a postpartum curettage for retained cotyledons, a complication thought to be common, but which can largely be obviated by exploring the uterus following manual removal to make sure that all fragments have been removed, particularly if there is any question that the placenta is not intact.

One patient died one month post partum of a pulmonary embolus. Another required a hysterectomy on the fourth postpartum day for an infected myoma. The remainder of the patients, except for those with morbidity, had uneventful postpartum courses.

L. Placenta.—The great majority of the placentas which were manually removed were normal, and the indications for removal of these placentas approximate those in the series as a whole (Table XV).

TABLE XV. THE PLACENTA AND INDICATIONS FOR MANUAL REMOVAL

			INDICATION					
			RETENTION		BLEEDING		PROPHYLACTIC	
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Normal	267	70.8	123	46.1	59	22.1	85	31.8
Infarcts	29	7.7	10	34.5	7	24.1	12	41.4
Twin	18	4.8	2	11.1	3	16.7	13	72.2
Placentitis	16	4.2	9	56.3	2	12.5	5	31.2
Placenta previa	12	3.2	-	-	4	33.3	8	66.7
Circumvallate	7	1.9	-	-	2	28.6	5	71.4
Succenturiate lobe	6	1.6	4	66.6	1	16.2	1	16.2
Velamentous cord	5	1.3	3	60.0	-	-	2	40.0
Bi- or tripartite	5	1.3	5	100.0	-	-	-	-
Hematomas	4	1.1	1	25.0	-	-	3	75.0
? Accreta	4	1.1	1	25.0	3	75.0	-	-
Girdle	2	0.5	1	50.0	-	-	1	50.0
Choriofibroma	1	0.3	-	-	-	-	1	100.0
Premature separation	1	0.3	-	-	-	-	1	100.0

The abnormal placentas which were most frequently removed on the indication of retention were those with bi- or tripartite characteristics, succenturiate lobes, or evidence of infection. It seems that the normal, thick, discoid placenta separates readily when the postpartum uterus contracts, but that those placentas whose cotyledons are spread thinly over a greater area of the fundus are capable of diminishing in size as the uterus contracts, and do not as readily dissect free.

TABLE XVI. SUBSEQUENT OBSTETRIC HISTORY

	CASES	PER CENT
Normal delivery	86	73.5
Abortion	15	12.8
Manual removal of placenta	9	7.7
Cesarean section	4	3.4
Ectopic pregnancy	2	1.7
Death in seventh month	1	0.9

There were four placentas in which there was a question raised as to the possibility of accreta. The indication for removal was retention in only one case, the remainder were removed because of bleeding.

M. Subsequent Obstetrical History.—There were 92 patients who had a total of 117 pregnancies followed in this hospital (Table XVI).

In one case, a subsequent cesarean section was followed by hysterectomy because of placenta accreta. The previous manual removal had been for retention of the placenta for over four hours, with the finding of an incarcerated, but separated placenta.

To evaluate the patients who had manual removal in subsequent pregnancies, one should consider the indication for the first and the subsequent procedure. Where one or the other procedure was done on a prophylactic basis, there would be, in most instances, no logical connection between the two (Table XVII). On this basis, there are only 5 cases (4.3 per cent) in which an indicated removal occurred for the second time. Perhaps the same defective physiology was responsible in the recurrent bleeding and retention. Two of these patients had normal deliveries as well as subsequent manual removal.

TABLE XVII. INDICATION FOR SUBSEQUENT MANUAL REMOVAL

INITIAL INDICATION		SUBSEQUENT INDICATION		
		RETENTION	BLEEDING	PROPHYLACTIC
Retention one hour or more	4	4	-	-
Excessive bleeding	3	-	1	2
Prophylactic	2	-	-	2

Therapy

A. General.—Until recent years on the ward service, there has been no specific therapeutic regime followed in cases where manual removal has been performed. Some measures of therapy were given in a majority of cases. In the earlier years, this was limited to intravenous fluids and blood, but with the advent of antimicrobial therapy in 1939, these agents have come into universal use. Since 1945, every patient who has received any type of therapy has received antimicrobials as well.

TABLE XVIII. THERAPY AND MORBIDITY

	CASES	PER CENT	MORBIDITY	
			TOTAL PER CENT	PUERPERAL PER CENT
Infusion	39		71.8	43.6
Infusion and blood	46		78.3	54.4
Infusion, blood and antimicrobials	46	58.6	50.0	34.8
Antimicrobials alone	67		13.4	4.5
Antimicrobials and infusions	7		28.6	28.6
Blood alone	16		56.3	18.8
No therapy	156	41.4	38.5	18.6

No conclusions can be drawn from morbidity figures following the various forms of therapy, for, especially in the earlier years of the series, the cases receiving active supportive measures were only those which appeared to warrant them. Where antimicrobials were used, the incidence of morbidity was lower (Table XVIII).

TABLE XIX. SHOCK AND ITS THERAPY

	CASES	PER CENT
Intravenous fluids	66	85.7
Blood	49	63.6
Intrauterine pack	18	23.4
Gum acacia	4	5.2
Plasma	4	5.2
Caffeine	4	5.2
Oxygen	3	3.9
None	2	2.6

B. Shock.—Signs of shock were noted during and after the procedure in 77 cases (20.4 per cent). Two of these patients died. In one of these fatalities, there was a 45-minute delay in starting blood; in the other, no blood was given due to technical difficulties.

TABLE XX. USE OF BLOOD IN SHOCK

	NO. OF CASES IN SHOCK	NO. OF CASES TRANSFUSED	PER CENT
1932-1938	41	19	46.3
1939-1949	36	30	83.3

The therapy used to combat shock is listed in Table XIX. In recent years, blood and intravenous fluids have been routinely used in the treatment of shock with emphasis on the early and rapid replacement of blood loss (Table XX).

Fig. 4.—Use of blood and antimicrobial agents after manual removal of the placenta.

C. Uterine Packing.—Intrauterine packs were used following manual removal of the placenta in 33 cases (8.8 per cent). The indication for the packing was either hemorrhage or shock. Since 1940, packs have been used only 8 times, and not at all since 1946.

TABLE XXI. INTRAUTERINE PACKS AND MORBIDITY

DURATION OF PACKING	CASES	MORBIDITY			
		PUERPERAL		TOTAL	
		CASES	PER CENT	CASES	PER CENT
Less than 12 hours	9	5	55.6	7	77.8
12 to 24 hours	14	11	78.6	12	85.7
Over 24 hours	9	3	33.3	7	77.8

The incidence of morbidity accompanying uterine packing is high, and occurred regardless of the time the pack remained in place, whether it was less than 12 or more than 24 hours. One of the patients whose uterus was packed died an hour later in irreversible shock (Table XXI).

D. Blood Transfusion.—The use of whole blood has become routine where blood loss has been excessive or shock has appeared. Prior to 1938, there was considerable delay before transfusion, but in recent years blood has been started almost immediately when needed. Ninety-eight patients (23.3 per cent) received blood transfusions. Hemorrhage had occurred in 70 of these (Fig. 4).

E. Antimicrobials.—Prior to 1938, there were no antimicrobials available for use. Since that time, these agents have become plentiful and inexpensive, and have been employed more and more frequently (Fig. 4). Penicillin alone seems to be the drug of choice, although its use in conjunction with the sulfonamides was formerly popular. The routine use of these drugs has been a major factor in the reduction of morbidity following manual removal.

Present Procedure for Manual Removal of the Placenta

A. Retention in the Absence of Bleeding.—If the placenta fails to separate within 30 to 45 minutes of delivery, or after the episiotomy is repaired, preparations are made for manual removal. Separation is often best determined by digital palpation through the cervix. Blood is drawn for typing and cross-matching and 500 c.c. of compatible blood are obtained and brought to the delivery room. An infusion of molar lactate is started in the arm through a transfusion set with a No. 18 needle. The patient is reprepared and redraped while the operator changes his gown and dons a version cuff. Anesthesia is induced with either nitrous oxide-oxygen-ether or Pentothal Sodium. The latter is quite suitable being quick acting and short lasting, although some operators feel that it is difficult to get adequate relaxation with it. The hand and arm are introduced slowly through the vagina into the uterine cavity. The placental edge is located, and, if the hand is within the amniotic sac, the membrane is penetrated. With the other hand on the fundus externally as a guide, the placenta is dissected from the uterine wall by opening and closing the fingers in scissors fashion until the whole placenta is free. Fifteen minims of Pitocin are now added to the infusion, and the hand grasping the placenta is slowly withdrawn, allowing the uterus to contract down behind it. The placenta is carefully examined and if parts appear to be missing, the cavity is re-explored. The infusion with the added Pitocin is allowed to drip slowly and the patient is observed for an hour or so on the delivery floor. Penicillin 400,000 units is given routinely for at least three days. If the blood loss appears excessive or the patient seems shocked, blood is given immediately.

B. Excessive Bleeding.—In the event of active bleeding prior to completion of the third stage, the above orderly procedure cannot be followed of necessity. Anesthesia is maintained or immediately induced. A gloved hand is introduced into the uterine cavity for exploration and the placenta is removed manually, followed by bimanual hemostasis. Blood is drawn for typing and cross-matching, and an infusion started as soon as possible. If necessary, type O Rh-negative blood from the emergency supply on the delivery floor is given. If the bleeding is slight but continuous, the precautionary measures outlined in the first paragraph should be followed as closely as possible, but without delay.

C. Modification.—A modification of this procedure consists of attempting, prior to manual removal, to get spontaneous expulsion of the placenta by using Pitocin in the infusion to stimulate uterine contractions. This has the greatest chance of success when the placenta is separated or only slightly adherent but incarcerated. It has the apparent advantage of minimizing blood loss, but some feel that it makes manual removal more difficult should it eventually be necessary.

Summary

Three hundred seventy-seven cases of manual removal of the placenta at the New York Lying-In Hospital have been reviewed, an incidence of 0.7 per cent of 53,645 deliveries.

Death occurred in 3 cases (0.8 per cent), but none of these fatalities can be directly attributed to the procedure.

The puerperal morbidity during this 18 year period in these cases has been 25.1 per cent, but has been declining steadily. The total morbidity for the same period has been 43.1 per cent.

Hemorrhage was associated with 127 cases (33.7 per cent); its occurrence has also decreased.

The principal indications for manual removal have been retention for one hour or more and excessive bleeding in the third stage. The procedure has also been done prophylactically to shorten the third stage or to facilitate a repair of a cervical or sulcus laceration.

At the time of manual removal, the placenta was found to be completely adherent, partially adherent, or free, in the presence or absence of uterine constriction. No placenta accretas were found in this series, although some densely adherent placentas were encountered.

Possible factors relative to the etiology of retained placenta and bleeding in the third stage have been discussed.

A survey of therapy given has been made, and the present procedure of manual removal has been described.

Conclusions

1. The incidence of manual removal of the placenta is low, and could be lower with better or more experienced management of the third stage.

2. Manual removal of the placenta is an operative procedure which carries with it a higher incidence of hemorrhage and morbidity than spontaneous expulsion of the placenta, and cannot be considered a preferable procedure.

3. Any factor causing excessive bleeding in the third stage or which tends to cause prolonged uterine contraction will tend to increase the incidence of manual removal. Manipulation of the fundus prior to expulsion of the placenta and general anesthesia are factors in excessive bleeding. The use of oxytocics prior to completion of the third stage decreases bleeding, but increases the incidence of incarceration of the placenta.

4. Manual removal of the placenta is indicated without delay in the event of bleeding during the third stage, or after retention for a period of time in the absence of bleeding. Manual removal of the adherent placenta after proper preparation is preferable to violent fundal manipulation in attempts to express the placenta from the uterus.

5. With judicious management, prompt blood replacement and prophylactic antimicrobial agents, manual removal of the placenta can be performed with a minimum of hazard and subsequent morbidity.

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525 East 68th Street

MARGINAL PLACENTAL BLEEDING

Anatomical and Pathological Considerations

BRUCE A. HARRIS, JR., M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, State University of New York, at New York City, College of Medicine and Kings County Hospital, and the Department of Obstetrics, Johns Hopkins Hospital)

DURING the past four years obstetricians have become increasingly aware that many cases of antepartum hemorrhage do not fit the classical criteria for either placenta previa or abruptio. The marginal placental sinus has been suggested as a possible source of this bleeding.

Two authors (Eastman[1] and Greenhill[2]) have recently made reference to clinical bleeding from the marginal sinus. The most extensive investigation of this syndrome, by Fish and associates[3] appeared in 1951. These authors state that "rupture of the marginal sinus of the normally implanted placenta was found to be responsible for one-third of all cases of antenatal hemorrhage occurring in the last trimester or in labor." Sexton and co-workers[4] describe a similar incidence from the Boston Lying-in Hospital. It is the purpose of this study to inquire further into the anatomical and pathological features of marginal placental bleeding.

Anatomical Considerations

Despite the vital importance of the placenta, its circulation, especially on the maternal side, is very poorly understood. This lack of knowledge stems from a paucity of adequate material; a human placenta in situ, fully attached, particularly at term, is a very rare specimen. Normally, placental separation begins at the margin almost as soon as the fetus is removed. The delivered placenta is inadequate for studies relative to the maternal circulation. Moreover, the delivered placenta is seldom carefully handled and almost never intensively studied.

Spanner's[5] classic on human placental circulation appeared in 1935. This author studied ten placentas in situ, as well as a large number of fresh specimens, mainly by corrosion preparations made after suitable injection of the maternal arteries and veins. Spanner states that the maternal blood enters the intervillous space from the decidual arterioles, and rises toward the chorion, where it collects in the "sub-chorial blood lake." Thence the blood flows to the periphery, where it drains into the maternal veins. At the margin is located the marginal sinus, a modified portion of the intervillous space. The sinus contains few chorionic villi. It is bounded superiorly by the chorion, inferiorly by the decidual plate, and laterally by the confluence of chorion and decidua in the closing ring of Waldeyer. Medially, the sinus may have a complete boundary, consisting of a marginal septum; or no boundary at all. Thus it is not a completely circumscribed blood vessel in the sense of the vena cava. The sinus is intermittently drained by large maternal veins.

Spanner concluded that the entire venous drainage of the placenta took place at the margin into the "uteroplacental veins of the marginal zone." The

complete correctness of this conclusion is now widely disputed. Indeed, the very existence of the marginal sinus as a constant placental structure has been questioned.[6]

Routine study of delivered placentas will conclusively demonstrate the marginal sinus, both grossly and microscopically, in every case. In any freshly delivered placenta, close inspection of the margin will show numerous openings, 1 to 2 cm. in diameter, in the decidual plate at the periphery of the maternal surface, where the membranes join the decidua. A probe may easily be passed through one of these openings, demonstrating that a peripheral circular sinus does exist.

The precise role of the marginal sinus in placental venous drainage is obscure. Since studies on the term placenta are as yet inadequate, the role of the sinus in normal labor at term must still be subject to conjecture.

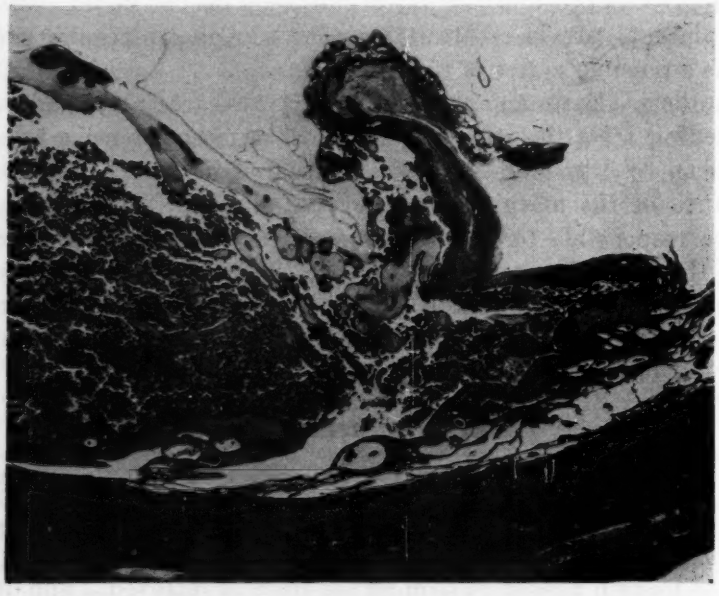

Fig. 1.

The present study embodies observations upon three placentas in situ. Specimen No. 1 shows a circumvallate placenta, previously described by Dees-Mattingly[7] and loaned to us through the kindness of the Department of Anatomy, Tulane University. This specimen was not injected. It is derived from a pregnancy of about twenty weeks' gestation, removed in situ with the uterus for intercurrent disease. Fig. 1 shows the marginal area of this placenta. The circumvallation is clearly demonstrable. At the periphery, the marginal sinus is readily identifiable as an area poor in chorionic villi. A very large venous channel leads into the myometrium from the inferior portion of the sinus, running centrally. This is a true vein, having been demonstrated by serial section. Especially notable is the great size of the venous channel and the apparent fragility of its walls. It is easy to imagine that an increase in uterine venous pressure might cause extravasation of the blood from such a large channel, and marginal separation. The area at the extreme right of the placenta, which apparently shows venous drainage into the decidua from the upper portion of the sinus in a region peripheral to the circumvallation, is actually an artifact.

Fig. 2 shows a similar picture in a noncircumvallate placenta. This specimen, No. 2, was obtained at autopsy from a patient who died of a brain tumor in the thirtieth week of her pregnancy. The uterus was injected with India ink through the arteries before being fixed and opened. The marginal sinus is

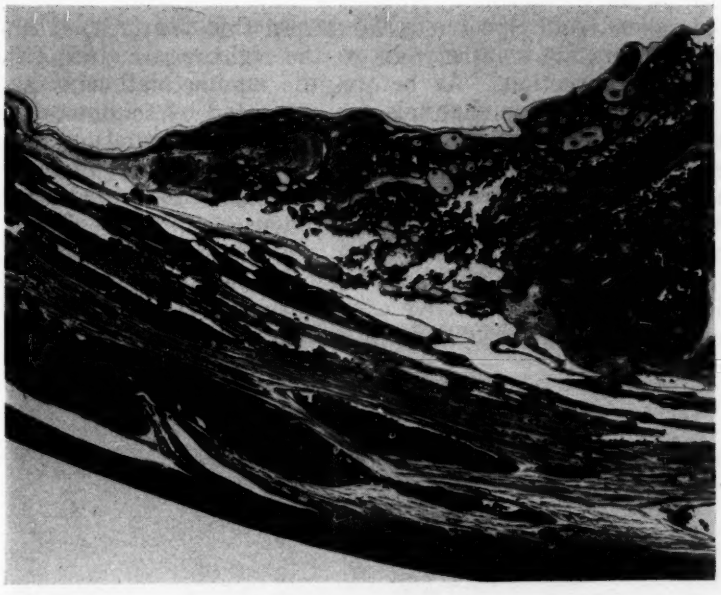

Fig. 2.

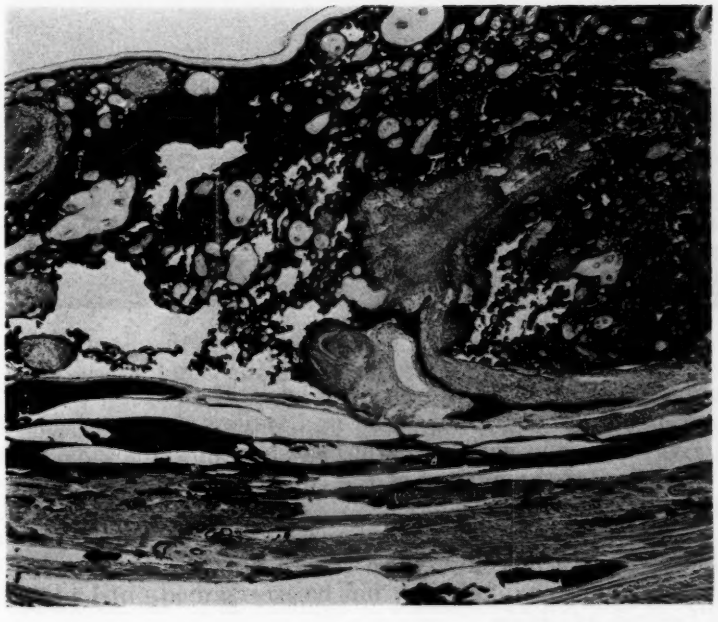

Fig. 3.

recognizable at the periphery. Especially noteworthy is the very large venous drain, in which the bottom of the sinus literally drops out. Serial sections have shown this to be a true vein, connecting with the great sinuses of the myo-

metrium. Also visible at the right is a small vein draining the intervillous space. As in the previous figure, the great size of the venous channels and the relative fragility of their walls is striking. The marked dilatation of the myometrial veins in this specimen is interesting, as compared with that in the preceding and following specimens.

Fig. 3 is taken from Specimen No. 2. In this view, the bottom does not drop out of the sinus. A smaller vein, at the right, again drains the marginal sinus in a central direction. As before, the myometrial veins are markedly dilated and the great venous channels are separated by tenuous decidual walls.

In contrast, Fig. 4 represents an entirely different situation. Specimen No. 3 is a placenta in situ of about 20 weeks' age. Hysterectomy was performed upon the mother for intercurrent disease. The marginal sinus is again clearly outlined. At the base of the sinus, a small venous channel is visible. This again has been traced through serial sections and shown to be a true vein. Notable in this specimen is the entire absence of the dilated myometrial veins described in the previous specimen. Extensive examination of this entire specimen shows a great paucity of venous drains from the marginal sinus.

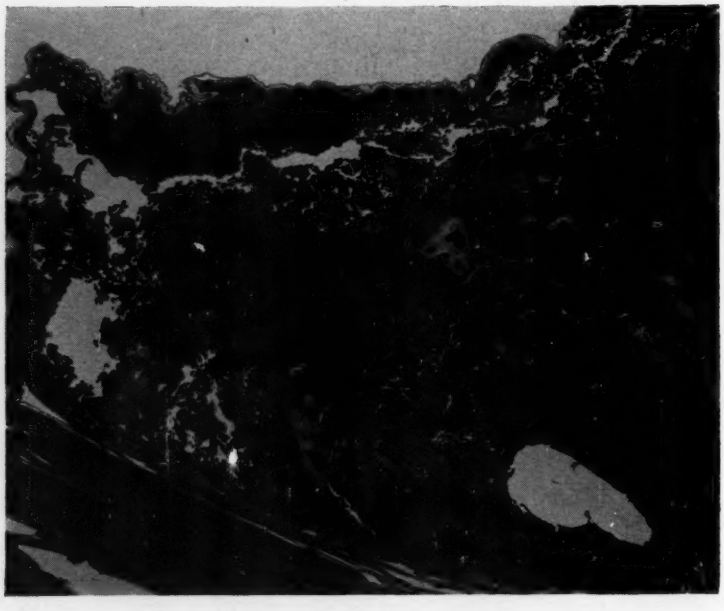

Fig. 4.

It is impossible to generalize upon the basis of these specimens. They do, however, show a definite marginal sinus and venous drainage channels leading from it. The variations in caliber of the myometrial veins may be artifacts related to the condition of the patient at the time of death or to the circumstances of the injection.

It now appears generally agreed that some central basal venous drainage takes place in the human placenta. The rate of flow and the proportion of blood drained through various channels may not be ascertained until adequate methods and material become available.

Pathological Considerations

Gross and microscopic pathological criteria have never been adequately defined for the diagnosis of marginal placental bleeding. The marginal sinus

normally is avulsed to some degree during delivery. Moreover, examination of freshly delivered placentas will show blood clots on the maternal surface in practically every instance. Hence, the diagnosis of pathological intrapartum marginal sinus rupture is contingent upon the discovery of a rent or slit in the marginal sinus wall, with a thrombus in the sinus at the point of rupture. This was first pointed out by Fish and associates.[3] This finding is frequently associated with the presence of a massive and adherent marginal clot with flattening of the underlying cotyledons.

In cases of marginal hemorrhage, microscopic examination will show the marginal sinus to be distended by a laminated, decolorized, and possibly partially organized old blood clot. A rupture through the decidual plate may be visible, depending upon the area sectioned. It appears that rupture of the marginal sinus always takes place through its decidual wall. Old hemorrhage in the marginal area of the decidual plate, with decidual necrosis, leukocytic infiltration, and phagocytosis, will be found.

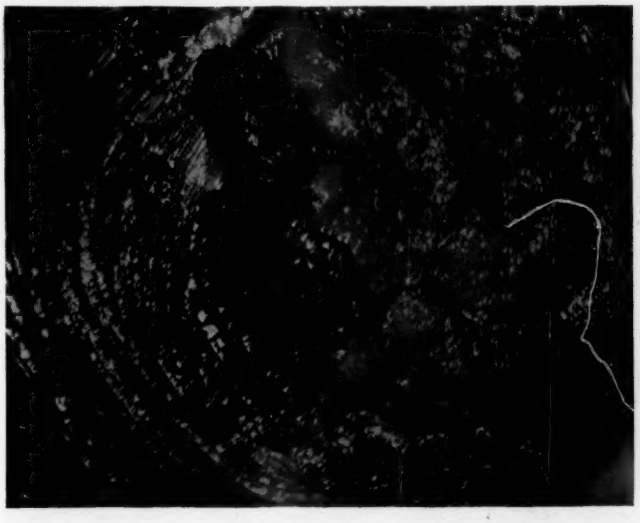

Fig. 5.

The pathological changes in the placenta are governed by the time at which the hemorrhage occurred. Obviously, hemorrhage occurring just prior to delivery is less likely to show these changes than a hemorrhage which occurred during or prior to the first stage of labor. Moreover, an extensive effusion of blood may so alter the anatomical landmarks that the only diagnosis which may be made is that of abruptio. Trauma to the placenta during delivery may result in complete destruction of the sinus and the avulsion of any adherent clot. Rough handling of the placenta may make accurate study impossible. It is thus self-evident that the diagnosis of marginal sinus rupture will often be no more than conjecture. In these instances, the only diagnosis possible is that of marginal separation. In this series infarcts have not constantly been found to adjoin the site of hemorrhage.

Fig. 5 shows the maternal surface of a full-term placenta in which the diagnosis of marginal sinus rupture was made. The very large clot is entirely marginal and arose from a series of ruptures in the sinus underlying it. The adjoining cotyledons were flattened. Rupture of the membranes was central.

Figs. 6 and 7 show the marginal areas of two placentas. In both, the marginal sinus is markedly distended by old partially organized clot. In Fig.

6, particularly, there is marked hemorrhage in the decidual plate adjacent to the marginal sinus.

Fig. 8 shows a portion of the maternal surface of a circumvallate placenta with antepartum clot adherent to the decidual plate, just peripheral to the area of reflection of the membranes. Fig. 9 shows a close-up view of a placental margin. The adherent blood clot which previously overlay this area has been

Fig. 6.

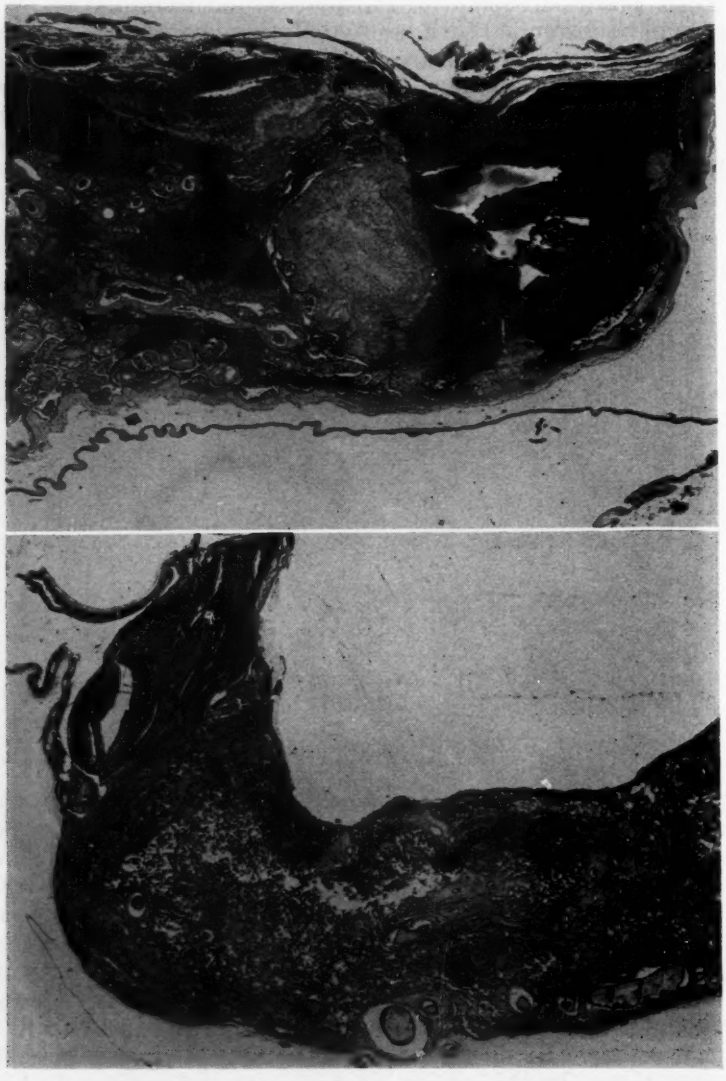

Fig. 7.

dissected free. Two major ruptures in the marginal sinus are revealed: at the right and left, old thrombus is visible in the sinus. Figs. 10 and 11 are close-up views of the decidual plate showing necrosis, polymorphonuclear infiltration, and hemorrhage.

Frequently the diagnosis of marginal sinus rupture cannot be made with certainty. Therefore, we have attempted to grade our specimens, so that in the

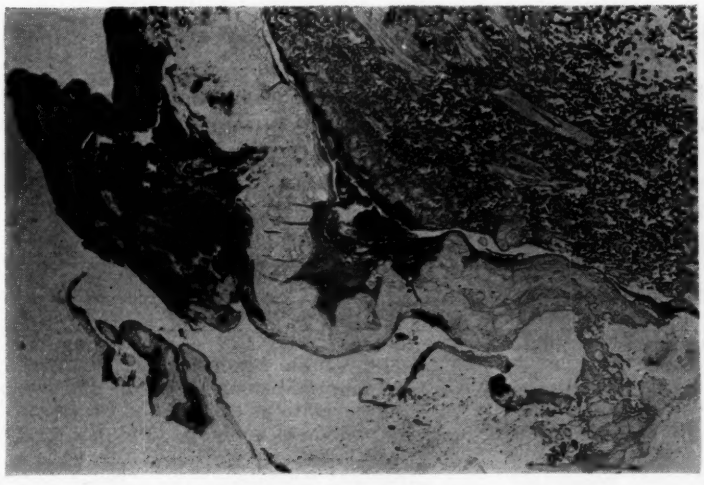

Fig. 8.

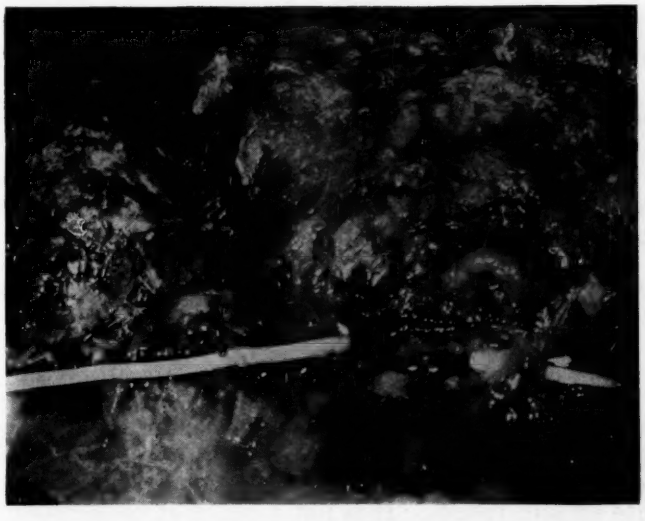

Fig. 9.

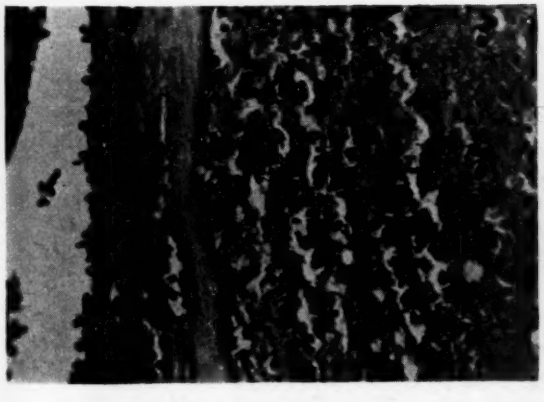

Fig. 10.

Fig. 11.

future a more accurate statistical evaluation may be possible. Table I shows the grading.

It will be obvious that certain cases of abruptio begin centrally. If the effusion of blood is sufficiently great, a large portion of the placenta, including the margin, may be dissected away. The site of origin of the hemorrhage may be obscure. In this series, Grade I has been restricted to specimens showing purely marginal bleeding.

TABLE I. GRADING OF PATHOLOGICAL FINDINGS

GRADE	DESIGNATION	GROSS FINDINGS	MICROSCOPIC FINDINGS
1	Ruptured marginal sinus	Adherent marginal clot, visible rupture of marginal sinus adjacent to clot, thrombus in marginal sinus	Aging of clot, decidual hemorrhage, polymorphonuclear infiltration, phagocytosis
2	Marginal separation	Adherent marginal clot, sinus cannot be identified in affected area	Same as Grade 1
3	Possible marginal separation	Marginal clot of questionable age, sinus not involved or not demonstrated	Signs of aging of clot not present
4	Antepartum bleeding of unknown origin	None	None

In the circumvallate placenta, both the superior and inferior walls of the sinus may be composed of decidua and identification of the sinus following delivery may be impossible. However, in a substantial number of these cases, blood clot showing signs of aging is demonstrable just peripheral to the area of reflection of the membranes.

Clinicopathological Considerations

As a part of this study, a series of 51 unselected cases of antepartum bleeding was collected at the Johns Hopkins Hospital and the Kings County Hospital. This series is obviously too small for accurate statistical evaluation. It may, however, indicate certain trends. It is not a series of consecutive cases of antepartum bleeding, but rather comprises those cases of antepartum bleeding which became available to the author, without reference to the clinical diagnosis.

Table II shows the relationship between the infant mortality, the weight of the infant, and the pathological grade of the placenta.

A substantial number of the patients included in this series showed some degree of blood pressure elevation. Table III shows the relationship of toxemia to the pathological changes found in the placenta. Among the thirteen patients who showed some degree of toxemia, three babies were lost.

In placenta previa, the bleeding is sometimes caused by separation at the margin. The diagnosis of placenta previa was made in five cases; three of these were graded 1 or 2 and one of these three infants was lost. The remainder were graded 4: all these babies survived.

In the entire series of 51 cases, symptomatology was extremely variable. The type of bleeding ranged all the way from repeated small hemorrhages throughout pregnancy to massive bleeding just prior to delivery. The classical signs of abdominal pain and uterine tenseness occurred in five cases, all of which were grade 1 or 2. Only one of these babies survived. The remaining patients had symptomless bleeding, the only pain being that associated with uterine

contractions. Infiltration of blood into the myometrium, as described by Couvelaire, occurred in one case. This patient had an intractable postpartum hemorrhage, requiring hysterectomy.

TABLE II. INFANT MORTALITY IN RELATION TO WEIGHT OF INFANT AND PATHOLOGIC GRADE

GRADE	NO. OF CASES	400-1,500 GRAMS		1,500-2,000 GRAMS		2,000-2,500 GRAMS		OVER 2,500 GRAMS	
		SURVIVED	DIED	SURVIVED	DIED	SURVIVED	DIED	SURVIVED	DIED
1	17	1	2	2	2	3	0	6	1
2	26	0	2	2	4	4	2	12	0
3	4	1	0	0	0	0	0	3	0
4	4	1	0	0	0	1	0	2	0
Total	51	3	4	4	6	8	2	23	1

Accurate evaluation of the amount of bleeding is almost impossible, because, in many cases, bleeding occurred at home. Clinical estimates as to the amount of blood on the clothing and bed linen are unreliable. In general, however, the infant mortality did not appear to be related to the volume of blood lost.

TABLE III. RELATION OF TOXEMIA TO PATHOLOGIC CHANGES

TYPE OF TOXEMIA	GRADE			
	1	2	3	4
Chronic hypertension	2	3	1	1
Chronic hypertension with pre-eclampsia	2	3	0	0
Pre-eclampsia	0	1	0	0
Total	4	7	1	1

Six patients were delivered by cesarean section; four of these placentas were grade 1 or 2. Of these, two infants died. The remaining two cases were grade 4; both infants survived.

Summary

Anatomical studies upon three placentas in situ have been presented, indicating that a marginal sinus exists in these specimens and communicates with the maternal venous system. An attempt has been made to establish gross and microscopic criteria for the diagnosis of marginal sinus rupture and marginal placental bleeding. In a small and unselected series of cases of antepartum bleeding, 82 per cent showed evidence of either marginal separation or actual marginal sinus rupture, with a fetal mortality of 28.6 per cent. Among 44 infants weighing over 1,500 grams, nine babies were lost, a mortality of 20.5 per cent. Only five patients showed the classical signs of premature placental separation.

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451 CLARKSON AVENUE

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

LEROY R. WEEKES, M.D., UMBERT E. ANZ, M.D., AND EDWIN B. WHITING, M.D.,
LOS ANGELES, CALIF.

(From the Department of Obstetrics and Gynecology, Queen of Angels Hospital)

PRIMARY carcinoma of the Fallopian tube is considered a rare gynecological entity, making up approximately 0.5 per cent of all female genital tract malignancies. Seventy per cent[1] are reported as unilateral growths. The total number of cases to be found in the literature is listed as 486.[2] However, many cases have undoubtedly not been reported in the past, and new cases are being reported with such increasing rapidity that the incidence of this disease may be more frequent than suspected.

So little is known about the subject that the average surgeon does not consider its possibility as a preoperative diagnosis. In fact, Hu, Taymor, and Hertig[3] in their review of the literature found that the diagnosis had been made preoperatively on only two occasions, and they added one case of their own in which a probable diagnosis of tubal carcinoma had been made. Since it is most often confused with pelvic inflammatory disease, a condition which is universally treated conservatively, most cases come to surgery in a late stage. The most common presenting symptoms—vaginal discharge, pain, and tumor—can hardly be considered diagnostic. The most characteristic symptom complex, hydrops tubae profluens, that is, profuse vaginal discharge accompanied by relief of pain and disappearance of a mass, is found in surprisingly few cases.

It is the purpose of this paper to review a small series of cases culled from the records of the Queen of Angels Hospital and compare these cases with the experiences of previous investigators.

Materials and Methods

All of the gynecological malignancies occurring at the Queen of Angels Hospital during the ten and one-half year period from July, 1941, to January, 1952, were reviewed; and only cases of primary carcinoma of the Fallopian tubes meeting the criteria established by previous investigators, Finn and Javert,[4] Hu, Taymor, and Hertig,[3] and Stern and Hanley[5] were selected.

Briefly, these criteria can be summarized as follows:

1. Grossly the main tumor is in the tube.
2. No primary lesion can be demonstrated in the ovary, endometrium, or any other organ.
3. Microscopically, the tubal mucosa is chiefly involved. If the wall of the tube is involved to any appreciable degree, a change in the mucosal lining from normal to malignant epithelium must be demonstrated.

Using these criteria, seven cases were collected for this study, six of which were unilateral, and one, bilateral.

Incidence

The incidence of primary carcinoma of the Fallopian tube varies in the literature from 0.16 per cent to 0.5 per cent of primary pelvic malignancies, as recorded in Table I. In the period covered by this report, 7 cases of primary carcinoma of the Fallopian tube were found among 640 primary pelvic malignancies for an incidence of 1.09 per cent.

TABLE I. INCIDENCE OF CARCINOMA OF FALLOPIAN TUBE

AUTHOR	CLINIC	PRIMARY PELVIC CARCINOMA	TUBAL CARCINOMA	
			NO.	INCIDENCE
Lofgren, Dockerty[6]	Mayo Clinic	10,000	16	0.16%
Haupt[7]	Bonn	1,361	3	0.22%
Hu, Taymor, and Hertig[3]	Free Hospital	3,878	12	0.31%
Emge[8]	Stanford Lane	1,350	5	0.49%
Finn, Javert[4]	Woman's, N.Y.C.	952	5	0.50%
Weekes, Anz, and Whiting	Queen of Angels	640	7	1.09%

Clinical Data

Carcinoma of the Fallopian tube is primarily a disease of the middle-aged group, with an average age of 46.4 years.[14] However, three cases involving 18-year-old girls have been reported in the literature.[9, 10] In fact, infancy and prepuberty appear to be the only immune periods, as cases have been reported from 18 years to 80 years of age. The age distribution in this series, which is recorded in Table II, varied from 32 to 80 years, with an average age of 55 years.

Numerous authors have been impressed by the frequent association of sterility with primary carcinoma of the tube. In the present series, five, or 71 per cent, were nulliparous individuals.

The primary symptoms are also presented in Table II. The predominant symptom was pain, which was the chief complaint of five women. In one case, the pain was acute in onset and simulated acute appendicitis; one patient complained of low back pain, another of pelvic pressure, and two of generalized lower abdominal pain. Three women had menstrual irregularities in the form of menorrhagia or menometrorrhagia. One case of postmenopausal bleeding was encountered. One patient noticed a mass in the lower abdomen, and another complained of recurrent profuse vaginal discharge.

Physical examination revealed the presence of a pelvic mass in five, and a rectal mass (unrelated) in another. One patient had signs of peritoneal irritation in the right lower quadrant.

The preoperative diagnoses made were fibromyomas of the uterus, ovarian cyst, endometriosis, acute appendicitis, and carcinoma of the rectum.

The treatment consisted of total hysterectomy and bilateral salpingo-oophorectomy at the initial surgery in two cases, one of which also required sigmoid resection and sigmoid colostomy because of damage to the sigmoid during the operation. Another patient had a supracervical hysterectomy and removal of adnexa.

Two patients had salpingectomy performed initially, followed by total hysterectomy and unilateral salpingectomy and bilateral oophorectomy subsequently. In one case the secondary operation was done three days after the initial surgery. In the other case, x-ray therapy for a total of 1,800 r measured in air without back scatter was delivered to each of four fields of the anterior and posterior pelvis, immediately after the initial surgery during a three-week period. The size of the field was 12 by 15 cm. and the quality of radiation used is expressed by the half value layer of 0.96 mm. of copper. At the secondary

TABLE II. CLINICAL DATA ON PRESENT SERIES

CLINICAL FEATURES					TREATMENT			RESULT	
AGE (YEARS)	PARITY	SYMPTOMS	SIGNS	DIAGNOSIS PREOPERATIVE	SURGERY	X-RAY	METASTASES AT OPERATION	DEAD	ALIVE
32	0	Pain, low back Menorrhagia Mass	Mass	Fibromyomas of the uterus	Total hysterectomy. Bilateral salpingo-oophorectomy. Sigmoid resection and colostomy	Yes	Yes		10 months with recurrence
44	0	Menometrorrhagia Vaginal discharge	Mass	Ovarian cyst	Left salpingectomy. Then total hysterectomy. Salpingectomy and bilateral oophorectomy	No	No		14 months without recurrence
45	0	Pain, pelvic Menorrhagia	Mass	Endometriosis	Total hysterectomy. Bilateral salpingo-oophorectomy	No	Yes	Presumably dead	
55	0	Right lower quadrant pain	Peritoneal irritation	Acute appendicitis	Salpingectomy. Total hysterectomy. Bilateral oophorectomy. Salpingectomy	Yes	Yes	6 months	
58	0	Postmenopausal bleeding, pain, loss of weight	Mass	Ovarian cyst	Supracervical hysterectomy. Bilateral salpingectomy and left oophorectomy	Yes	Yes		3½ months
73	iv	Pelvic pressure Rectal bleeding	Rectal mass	Carcinoma of rectum	Abdominal perineal resection, left salpingectomy	No	Yes		20 months with recurrence
80	i	None	Mass	Ovarian cyst	Left salpingo-oophorectomy	No	No		1 month

surgery, performed 4 weeks after radiation therapy was completed, viable adenocarcinomatous infiltration of the right ovary was found.

The sixth patient had a salpingectomy and a combined abdominal perineal resection performed for a probable adenocarcinoma of the rectum. However, pathological sections revealed an adenocarcinoma of the tube and a benign villous adenoma of the rectum. No further surgery or x-ray therapy was given in view of the advanced age of the patient.

The final patient had a unilateral salpingo-oophorectomy performed. No subsequent surgery was deemed advisable because the patient was 80 years of age.

At operation, five patients, or 71 per cent, already had gross evidence of metastatic spread of the lesion. This emphasizes the tardiness with which these patients arrive at the operating table, due chiefly to the quiescent nature of the growth regarding clinical symptoms.

Case Reports

CASE 1.—(8089) R. W., a 45-year-old, white, gravida 0, housewife was admitted to the Queen of Angels Hospital on Sept. 30, 1945, with a history of pain throughout the lower abdomen and menorrhagia of unstated duration. Past history revealed an appendectomy and suspension of the uterus in 1943.

Physical examination was essentially normal except for pelvic examination. The uterus felt slightly enlarged. In the right adnexal area a cystic mass extending upward from the right half of the cul-de-sac was readily palpable. Laboratory examinations showed a 48 per cent hemoglobin, 2.9 million red blood cells, normal white blood count and differential, and normal urinalysis. Two transfusions of 500 c.c. of blood were given preoperatively.

Preoperative diagnosis was pelvic endometriosis.

At operation, papillary adenocarcinoma implants were found on the serosal surface of the pelvic organs. The right tube was greatly distended, measuring 15 cm. in length and 6 cm. in greatest width. The rest of the pelvic organs were normal in size. Tumor implants were present on the serosal surfaces of the bowel, and the omentum was thickneed to 2.5 cm. and contained numerous tumor nodules, the largest about 4 cm. in diameter. A total hysterectomy, bilateral salpingo-oophorectomy, and resection of the omentum were performed.

Pathological report revealed papillary adenocarcinoma in the right Fallopian tube, multiple peritoneal implants of papillary adenocarcinoma, and papillary adenocarcinoma metastatic to the omentum.

The postoperative course was afebrile and uncomplicated, and the patient was discharged on Nov. 3, 1945.

CASE 2.—(2948, 4397, 1241C) L. B., a 73-year-old, white, gravida iv, para iv, widow was admitted to the Queen of Angels Hospital on March 18, 1949, with a history of progressive pelvic pressure and rectal bleeding during bowel movements, of four months' duration. There was a weight loss of 3 pounds during the four months. No vaginal bleeding or discharge was noticed since her menopause 23 years previously.

Physical examination revealed hypertension with a blood pressure of 200/100. Pelvic examination revealed the vagina to be contracted and atrophic; the uterus, small and freely movable, and the adnexal areas, clear. On rectal examination, a round, fixed, soft, nontender mass 5 to 6 cm. in diameter was palpable, projecting into the rectal lumen approximately 2 inches above the anus.

Complete blood count and urinalysis were normal. The Kline test was negative. Total proteins were 7.0 per cent, nonprotein nitrogen 20 mg. per cent; bleeding, prothrombin and coagulation times were normal. Chest x-ray revealed a cardiac silhouette consistent with hypertension.

During her work-up in the hospital, a partial intestinal obstruction developed and a transverse colostomy was performed. Several omental nodules were found. A biopsy of one revealed undifferentiated carcinoma, Grade IV, metastatic to the omentum.

The patient was discharged on April 2, 1949, following an uneventful postoperative course and was readmitted April 26, 1949, for a combined abdominal-perineal resection for probable carcinoma of the rectum. During the second operation, a reddish-gray nodule 1 cm. in diameter was seen in the distal end of the left Fallopian tube, and two similar nodules were found on the lateral pelvic peritoneum adjacent to the left ovary. A left salpingo-oophorectomy was performed in addition to the abdominal-perineal resection. Pathological diagnosis was benign villous adenoma of the sigmoid colon, undifferentiated carcinoma of the Fallopian tube, metastatic undifferentiated carcinoma in nodules removed from pelvic wall similar to the carcinoma of the tube.

Postoperatively the patient developed a rectal abscess, which was drained. The transverse colostomy was closed and the sigmoid colostomy maintained. The patient was discharged on June 10, 1949.

She was readmitted Feb. 1, 1951, with nausea, vomiting, and ascites. Abdominal paracentesis yielded 2,350 c.c. of fluid. The pathological report was "peritoneal fluid containing many epithelial tumor cells (carcinoma)." There was slight symptomatic improvement, and the patient was discharged Feb. 10, 1951, with a diagnosis of generalized carcinomatosis secondary to carcinoma of the Fallopian tube.

CASE 3.—(9993) L. M., a 44-year-old, white woman, gravida 0, was admitted to the Queen of Angels Hospital on Sept. 11, 1950, with a history of menometrorrhagia of six months' duration and recurrent profuse yellowish, nonirritating, nonoffensive vaginal discharge of six months' duration. No weight loss was noticed.

Examination of the abdomen revealed a palpable, fixed, cystic mass in the left lower quadrant extending from the pelvis to half the distance to the umbilicus. Pelvic examination revealed the cervix and uterus to be normal. A large, fixed, cystic mass could be palpated, filling the cul-de-sac and extending in the left adnexal area, approximately 15 cm. in diameter. The right adnexal area was normal. Complete blood count and urinalysis were normal.

The preoperative diagnosis was left ovarian cyst.

At operation, the uterus and right adnexa were found to be normal. The left tube was markedly enlarged, retort shaped, measuring approximately 15 cm. in length and 5 cm. in maximum width. The fimbriated end of the tube was densely adherent to the cul-de-sac. A left salpingectomy was performed and the specimen was immediately sent to the pathologist, who made a tentative diagnosis of hydrosalpinx, on gross examination. Because the patient was recently married and desired to become pregnant, no further surgery was done. Microscopic examination, however, revealed primary carcinoma of the Fallopian tube.

Three days later, after preliminary catheterization of the ureters, a total hysterectomy, right salpingo-oophorectomy, left oophorectomy, excision of the parametria and most of the peritoneum covering the cul-de-sac were done. The postoperative course was uneventful. The patient was discharged on Sept. 25, 1950.

The patient and her husband refused postoperative x-ray therapy, so none was administered. At present, the patient is completely asymptomatic and free of any palpable recurrence.

CASE 4.—(5122, 7697) D. M., a 55-year-old, white, gravida 0, housewife was admitted to the Queen of Angels Hospital on June 18, 1942, complaining of right lower quadrant pain. The patient was apparently well until the day prior to admission, when she developed a sudden sharp pain in the right lower quadrant associated with nausea and intermittent vomiting. Some relief was obtained with an enema, but the pain had persisted as a dull, constant ache on admission. No vaginal bleeding or discharge was noticed. The age of cessation of menses was not stated.

Physical examination revealed rebound tenderness and rigidity in the right lower quadrant. Pelvic examination was negative. Complete blood count revealed 73 per cent hemoglobin, 4.2 million red blood cells, 13,100 while blood cells, with 85 per cent polymorphonuclear leukocytes.

Preoperative diagnosis was acute appendicitis.

At operation, the right tube was found to be enlarged and inflamed; the appendix was normal; the uterus contained a small subserous fibromyoma. Right salpingectomy, appendectomy, and myomectomy were performed.

Pathological report revealed carcinoma of the right Fallopian tube.

The postoperative course was uneventful and patient was discharged on June 28, 1942.

X-ray therapy consisting of 1,800 r to 4 fields over the anterior and posterior pelvic regions was administered between July 7 and July 30, 1942.

On Sept. 1, 1942, the patient was readmitted and total hysterectomy, bilateral oophorectomy, and left salpingectomy were performed. No evidence of metastases was seen at operation. Pathological diagnosis revealed carcinoma infiltrating the right ovary.

The postoperative course was uneventful, and the patient was discharged on Sept. 14, 1942.

CASE 5.—(3124) S. C., a 32-year-old, single, gravida 0, Negro woman was admitted to the Queen of Angels Hospital on March 20, 1951, with a history of a lower abdominal tumor mass of three years' duration, menorrhagia of two years' duration, and low back pain of one year's duration.

On abdominal examination, a firm, nontender mass was visible and palpable, extending from the symphysis pubis to the umbilicus. On pelvic examination, the mass appeared to be contiguous with the cervix and was thought to be an enlarged corpus uteri. The cervix revealed a mild erosion.

Laboratory findings consisted of a negative Wassermann test, normal urinalysis, 3.8 million red blood cells with 10.7 Gm. hemoglobin, and 9,000 white blood cells, with a normal differential.

The pre-operative diagnosis was fibromyomas of the uterus and chronic cervicitis.

At operation, performed at Queen of Angels Hospital on March 21, 1951, the uterus was found to be normal in size and shape. Posterior to the uterus and adherent to the posterior surface of the uterus and to the cul-de-sac and sigmoid colon was a mass of tissue consisting of both right and left adnexa which were intimately attached to each other. The adnexal masses were separated from each other and from their attachment to the cul-de-sac and sigmoid with much difficulty. During the separation, a copious amount of friable, soft, pale, reddish, papillary tumor tissue was encountered. A total hysterectomy and bilateral salpingo-oophorectomy and appendectomy were performed. A laceration was found in the sigmoid at the rectosigmoid junction where the tumor tissue had been adherent to the bowel. Because of the possibility of invasion of the bowel by the tumor, a sigmoid resection and sigmoid colostomy were performed. A Chaffin tube was inserted because of spillage of the bowel contents during this procedure. The postoperative course was uneventful and the patient was discharged on the ninth postoperative day.

On Nov. 27, 1951, vaginal bleeding was noticed. Examination of the vagina revealed friable tissue high in the vaginal vault which was reported as adenocarcinoma on biopsy. X-ray therapy was begun with a tentative schedule of 3,500 r to the pelvis through the vaginal cone and 8,000 r to the pelvis by external radiation.

CASE 6.—(13023) M. J., an 80-year-old, white, gravida i, para i, housewife was admitted to the Queen of Angels Hospital on Dec. 12, 1951. She had noticed no symptoms except a feeling of slight pressure on the rectum and bladder. She had gone to her physician for routine examination, and he had discovered a large abdominal mass, of which she had no cognizance. There was no history of vaginal discharge or bleeding of any type since her last menstrual period 30 years previously. She had a hypertension known since 1947 when she suffered a mild cardiovascular accident. She had had no previous surgery.

Physical examination revealed a woman appearing much younger than her stated age. Blood pressure was 200/100. There was cardiac enlargement and a right corneal opacity. Abdominally there was a large, firm, symmetrical, movable, nontender mass in the lower abdomen rising to the height of the umbilicus. On pelvic examination the vagina and cervix were found to be atrophic and the pelvis was filled with the large firm mass. The organs were not separately distinguishable.

Complete blood count and urinalysis were essentially normal.

The preoperative diagnosis was a large ovarian cyst.

At surgery on Dec. 14, 1951, a large, smooth, left ovarian cystic mass 12 cm. in diameter was found and removed. The Fallopian tube was attached to the external aspect and was slightly dilated. The remaining pelvic organs were not subjected to surgery. The appendix was removed. The other abdominal organs were explored and found to be negative.

The pathological report was (1) left tubovarian cyst; (2) papillary adenocarcinoma of the left Fallopian tube, Grade III. There was no involvement of the ovarian cystic mass.

The postoperative course was afebrile and uncomplicated and she was discharged Dec. 23, 1951. At the time of discharge her physicians were contemplating the use of radiation, further surgery being deemed inadvisable because of her age and hypertensive state.

CASE 7.—(8776) H. P., a 58-year-old, white woman married, gravida 0, para 0, was admitted to Queen of Angels Hospital Aug. 16, 1951, with a history of intermittent vaginal bleeding of two months' duration, pain in the lower abdomen, and loss of weight.

The patient's history revealed appendectomy and oophorectomy at the age of 19 years.

Family history revealed that the mother had died of cancer of the larynx.

The patient was well developed, well nourished, postmenopausal. The blood pressure was 128/100.

Pelvic examination revealed a small, atrophic uterus, a large cystic mass filling part of the pelvis, and a moderate amount of tenderness. Complete blood counts and urine examinations were normal.

The preoperative diagnosis was ovarian cyst.

At operation the uterus was small and atrophic. The right ovary was absent. The right tube was present and somewhat dilated, measuring 2 cm. in diameter. The left ovary was cystic, measuring 8 cm. in diamter. No evidence was seen of carcinoma extending to other abdominal organs, with the exception of numerous small rice-grain-size peritoneal implants. A supracervical hysterectomy, left oophorectomy, and bilateral salpingectomy were performed.

Pathological report was: (1) papillary adenocarcinoma of the Fallopian tube; (2) secondary carcinoma of the left ovary and endometrial polyp; (3) serous cyst of the left ovary; (4) fibromyomas of the uterus.

The postoperative course was uncomplicated and afebrile.

The patient received radiation to six fields covering the entire abdomen. Each received 2,000 r measured in air without backscatter. She made 40 visits. The quality of radiation used is expressed by ½ value layer of 0.92 mm. of copper. The patient had some radiation sickness throughout treatment but improved with the last visits. She was discharged on Sept. 22, 1951, in good condition.

As of Jan. 1, 1952 she was living, and in good condition and comfortable.

Comment

It would be difficult to find a disease which has eluded diagnosis as completely as tubal carcinoma. Diagnostic errors are frequent because of the rarity of the condition and because the symptoms of pain, vaginal discharge, and palpable tumor are not typical of this disease alone. They are associated more frequently with the more common genital lesions, pelvic inflammatory disease, fibroids, or ovarian cysts. Numerous writers have referred to hydrops tubae profluens (the relief of pain and disappearance of a tumor mass following a profuse vaginal discharge) as a symptom complex peculiar to this disease, and have reported its occurrence in varying incidences. Unfortunately, this symptom complex not only occurs rather infrequently but is not pathognomonic of carcinoma of the tube. It is a symptom of intermittent hydrosalpinx and may occur in association with any hydrops tubae with a patent uterine ostium.

Pain was the most prominent symptom in this series. Most authors agree that pain occurs early in the course of this disease, differing from carcinoma of

the uterus or ovary, where pain appears only after the carcinoma has spread beyond the limits of the organ primarily involved and has invaded nerve cells. The pain in carcinoma of the tube is the result of the tumor and its discharge being inclosed in a cavity which when distended causes tension in the wall, and pain. The resultant pain is usually intermittent, lancinating, cramplike, located unilaterally in either lower quadrant, and referred down the thigh or into the back. When the intraluminal pressure is sufficient to cause the tube to empty its contents through the uterine ostium, a profuse vaginal discharge together with a sudden relief of pain results. If the uterine ostium is closed tightly, the tube may empty itself through the fimbriated end, and peritoneal irritation may become evident with the acute onset of pain simulating an abdominal crisis requiring surgery. Symptoms of intestinal obstruction may later supervene from metastatic implants in the peritoneal cavity.

There was a nonspecificity of the character of the pain in this series. The presence of any pain in the pelvis which is unexplained by pelvic findings may be a clue even though the pain lacks the characteristic description usually applied to tubal carcinoma. In the present series the types of pain encountered were: acute right lower quadrant pain with nausea and vomiting, generalized lower abdominal pain, low back pain, and increasing pelvic pressure.

A vaginal discharge is reported to be the most common symptom of carcinoma of the tube. The vaginal discharge may be serosanguineous, yellowish, or creamy, and more or less continuous and unaffected by treatment. The most frequent form is the serosanguineous variety. Unless the discharge has a sanguineous component, the discharge may go unnoticed except by fastidious women, and medical attention may not be sought because of the mistaken belief that the discharge is "leukorrhea."

With extensive breakdown of the friable cancer tissue, the vaginal discharge may become bloody, giving rise to intermenstrual, more or less continuous, bleeding. Postmenopausally, the bleeding assumes the same lawless pattern. Menorrhagia alone may occasionally be encountered. The occurrence of menorrhagia can be explained only on the basis of associated pathology such as fibroids or pelvic inflammatory disease, or of metastatic spread to the uterus or ovaries. Menorrhagia occurred in two cases in this series and may be explained by the extensive involvement of the pelvic organs in these cases.

As to special tests, the diagnostic curettage is negative. Before the menopause the curettings will be of the type corresponding to the stage of the sexual cycle at which the dilatation and curettage are performed. The cause of the bleeding usually remains unknown.

Smears should be positive in cases of bleeding in about the same proportion as in cancer of the endometrium. Meigs[3] as far back as 1934 emphasized the importance of collecting every bit of discharge. This should be filtered and examined microscopically. The routine use of this procedure may result in the discovery of earlier cases of primary cancer of the tube.

Hysterosalpingography has been suggested as a diagnostic measure. No reported cases are available in which this measure was employed. The possibility of peritoneal contamination is very likely.

Exploration of the cul-de-sac by needle puncture was performed by Falk in 1898. Today, if pelvic malignancy were suspected, exploratory laparotomy would be performed rather than risk contamination of the peritoneal cavity. Culdoscopy has been suggested. Carefully and expertly done, it may uncover some early cases.

Differential diagnosis includes the usual garden variety of pelvic lesions—hydrosalpinx, pyosalpinx, ovarian cyst, and fibroids, particularly the pedunculated variety.

Early diagnosis and radical surgery comprise the treatment of choice. The chance for cure varies directly with the stage of the disease encountered and with the histological grading of the tumor. Hu and associates[3] have reported the highest over-all five-year survival rate of 40 per cent. They showed a fairly consistent correlation between the histological grading and prognosis, the well-differentiated papillary forms having a better prognosis. In this series, two have succumbed to the disease; two have had recurrences within one year of their original surgery; and of the remaining three, the time interval is too short to evaluate their prognosis.

Two cases of preinvasive carcinoma of the tube have been reported in the literature.[3, 13] These cases represent incidental findings in tubes removed for other pathology. The prognosis should be viewed with complete optimism in such cases, which are the exception rather than the usual findings at surgery. The majority of cases rarely come under treatment in a favorable stage. According to McGlinn and Harer,[15] the incidence of gross metastases at the initial surgery is 30 per cent. In this small series, the incidence was 71 per cent.

From a review of the literature, the following rules of thumb may be instrumental in arriving at an earlier diagnosis before contiguous organs or lymph glands have become involved:

1. A persistent vaginal discharge, not amenable to treatment, not explained by the usual etiological agents, and especially if serosanguineous, should be viewed with suspicion, and repeated vaginal smears should be made.
2. Any obscure pelvic lesion, especially in the fifth or sixth decade, requires surgical exploration.
3. Any unilateral mass in a menopausal or premenopausal woman, associated with irregular bleeding and a negative curettage, requires an exploratory laparotomy.
4. If no adequate cause has been found to explain irregular bleeding following a curettage, it is necessary to suspect carcinoma of the adnexa and particularly the tube.
5. Indiscriminate use of radium to arrest vaginal bleeding without a definite pathological diagnosis should be condemned.
6. More liberal use of vaginal smears is advisable, especially in the menacme, where the many benign conditions may cloud the picture.
7. Every enlarged tube should be opened and examined as soon as it is removed. in order that appropriate surgery can be accomplished without delay.

Although carcinoma of the Fallopian tube may spread by direct extension through the fimbriated end to the adjacent peritoneum, the most important role is played by the lymphatics. The uterus, ovary, and peritoneum may become involved because of their intimate lymphatic relationship to the tube. In addition, lymphatic extension to the iliac and lumbar glands or even the distant supraclavicular glands may occur. In less than a third of the cases bilateral tubal carcinoma may occur. Meigs states that the vagina may be involved in 60 per cent of the cases.

Because of the mode of spread, radical surgery with removal of the entire uterus, both tubes and ovaries, and wide excision of the parametria should be accomplished. The iliac and lumbar glands should be palpated for evidence of spread.

The advisability of postoperative x-ray therapy seems to be open to question. Most authors recommend the use of postoperative roentgen therapy but admit that the results are poor and the true value is unknown. In Case 4, active, growing carcinomatous tissue was found at secondary operation in spite of adequate postoperative radiation.

Summary and Conclusions

1. Primary carcinoma of the Fallopian tube is a rare gynecological entity. making up approximately 0.5 per cent of all female genital tract malignancies.

2. A review of the gynecological malignancies occurring at the Queen of Angels Hospital during the ten and one-half year period from July, 1941, to January, 1952, revealed seven cases of primary carcinoma of the Fallopian tube satisfying the established criteria.

3. The incidence in this series was 1.09 per cent.

4. Clinical data revealed an average age incidence of 55 years, associated sterility, and predominant symptoms of pain, pelvic mass, and vaginal discharge.

5. Seven rules of thumb are presented as an aid to earlier diagnosis.

6. The treatment in this series was varied. Because of the mode of spread, radical surgery, with the removal of the entire uterus, both tubes and ovaries, and wide excision of the parametria, should be accomplished. The iliac and lumbar glands should be palpated for evidence of spread.

7. The use of postoperative x-ray therapy is equivocal.

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2301 Bellevue Avenue

AMNIOTIC EMBOLI: DO THEY REALLY CAUSE SUDDEN DEATH IN OBSTETRICS?

BENNO TUNIS, M.D., NEWARK, N. J.

THE first report of the existence of a new and strange cause of death during delivery (spontaneous or artificial) was published late in 1941. An amniotic embolus or emboli was described as the death-causing factor intra partum. It was a sudden death and no treatment was available to prevent it; in short, it was reported and considered as an unpreventable obstetrical death. Since that date some twelve additional articles, presenting altogether a total of 25 cases, have come to the author's attention, all of which fatalities have been attributed to amniotic emboli.

The author of this first report, Steiner,[1] presented eight cases of sudden and unpreventable obstetrical death which they claim was caused by an embolism of the liquid amnii into the capillaries of the lungs. This embolism occurred without warning and with lightning-like rapidity, killing the parturient instantly. First, there was a short spell of cyanosis associated with a very rapid pulse. Some of the dying had convulsions, all perspired and then were cold. There was no frothing of the mouth except in one case. Nearly all of the patients had either spontaneously or artificially ruptured membranes with a free discharge of amniotic fluid, partly clear, partly cloudy, and partly with a bad odor.

Considerable doubt or misgiving about such fatalities has prompted the writer to analyze and scrutinize these cases closely. He has never quite been convinced, first, that there was an amniotic embolus; second, that the amniotic embolus was the cause of the fatal outcome; and, finally, that there were not different causes operating to cause the death wrongly attributed, perhaps, to the amniotic emboli.

The author plans in this paper to take up these 25 cases one by one beginning with the 8 cases reported by Steiner and Lushbaugh in their order of presentation. He will comment case by case on the clinical picture presented and he will select both macroscopic and microscopic findings from the pathology which appear to him as especially significant and which by and large are responsible for the doubts entertained regarding the cause of death. He will conclude the consideration of each case with his own diagnosis or with a statement of opinion regarding the cause of death.

CASE 1.—A 30-year-old para ii entered the Illinois Central Hospital, Chicago, two weeks before term. There were no fetal heart sounds audible. The patient had moderate labor pains and was generally doing well. Suddenly she was awakened by extremely severe pelvic pain, air hunger, and profuse perspiration. She was in shock and became cyanotic. A macerated fetus was delivered spontaneously with ether anesthesia. The

placenta was expressed and the hemorrhage followed. The uterus was packed, the patient received 1,000 c.c. of saline solution as hypodermoclysis and, a little later, 500 c.c. of blood were given. She died two hours and 25 minutes after delivery. Postmortem examination revealed the organs very pale with a blood clot in the right atrium. Microscopically, the lungs showed foreign material in the arteries of 1 mm. size down to the arterioles. The masses occluding the vessels consisted of mucin.

Comment.—This appears to me as an embolism probably originating from the right atrium during a stage of shock and exsanguination.

CASE 2.—A 26-year-old primipara, at the Chicago Lying-in Hospital, suffered ruptured membranes after 13 hours of active labor. The dilatation of the cervix was slow. After 31 hours in labor, the patient, with a pulse of 146 per minute, vomited and began to perspire. She fell into a coma, received cardiac stimulants without success. She died undelivered about one hour after the first sign of collapse. Postmortem examination revealed acute pulmonary edema; frothy fluid from the cut surfaces of the lung; both right chambers were distended. A right hydronephrosis, macroscopically. Arterioles and capillaries of the lung were dilated and filled with mucinlike substances and contained leukocytes and epithelial squamae.

In my opinion, this death was caused by a sudden heart failure.

CASE 3.—Soon after a hard, short labor the patient went into shock to which she succumbed in eight and one-half hours. She had a relaxed uterus with moderate postmortem hemorrhage. The gross pathologic examination disclosed comparatively normal viscera, except for pulmonary edema. The authors, themselves, state that the examination did not entirely explain the death.

CASE 4.—After a severe labor the patient went into coma and a uterine hemorrhage developed. According to the authors, she died from an amniotic embolus and the hemorrhage seemed to follow the embolism (?).

Comment.—This was, quite correctly, a postpartum hemorrhage. And, in my opinion, the supposition of amniotic embolism was not based on factual evidence and the circumstances of the sudden death were not made clear.

CASE 5.—Following a pregnancy complicated by thyrotoxicosis that responded well to medical management, the patient had a sudden delivery following which she soon went into shock and died in fifty-five minutes. The lungs showed amniotic emboli in the capillaries. Complicating factors, according to the authors, were a hyperplastic thyroid and a chronic endocarditis.

In our experience, endocarditis is the most frequent cause of death during gestation. It very often produces emboli of its own and I would repeat that it is a "killer."

CASE 6.—A patient, two months past term, went into coma after severe labor. A postpartum hemorrhage followed. At autopsy, amniotic emboli with an acute sepsis were advanced as the cause of the death.

I contend here that the acute sepsis was the cause of death. It is not the embolism, amniotic or nonamniotic, which produces sepsis, rather the contrary.

CASE 7.—A diabetic patient died in shock two hours after delivery. The authors point to the complicating feature of pathologic changes commonly associated with eclampsia.

In my experience diabetes is a serious complication which, by itself, could explain the death.

CASE 8.—A woman with a fetus known to be dead, after two days of mild, intermittent pains, suddenly went into severe labor and quickly passed into shock, in which she died in about two hours. Autopsy disclosed a ruptured uterus with the fetus lying in the peritoneal cavity.

An unrecognized rupture of the uterus without proper treatment (which can only be surgical) always spells certain and sudden death.

By way of summation, Steiner and Lushbaugh present evidence in their attempts to establish the following: (1) that the amniotic embolus as a factor of sudden death in obstetrics was unknown up to the time of their report; (2) that there is a distinct pathological and anatomical basis for this type of fatality; (3) that the experimental production of this disease in animals has been demonstrated; and (4) that this newly discovered cause of sudden death "is composed of several obstetric complications which are widely known but whose etiology has been unknown up to the present time, like obstetric shock, postpartum uterine atony with hemorrhage, perhaps some conditions we used to call non-convulsive toxemia, and acute pulmonary edema of pregnancy." We would here ask the question, Shall we understand that amniotic emboli cause these conditions or that these conditions predispose to amniotic emboli? In this writer's opinion, these obstetric complications of which the embolic death is supposedly "composed" are far stronger (that is, more dangerous) and more important to recognize and treat, than the amniotic emboli!

At this point a brief review of the nature of an embolus may be pertinent. An embolus is a clot or other plug which after moving for some distance in the blood stream becomes impacted in a vessel. It may originate in the veins, in the heart, or in the arteries. The material which produces an embolus is a blood clot, a tumor cell, clumps of bacteria, fat globules, and air bubbles (recently added), liquor amnii and its contents. The composition of the amniotic fluid is liquid with very few cells and some chemicals from serum or body added, a few epithelium-like cells from the surface of the fetal skin, and some admixture of the secretions of the sebaceous glands of the skin of the fetus. Lanugo hairs, also, are found.

When the membranes rupture, the liquor amnii runs down according to the law of gravity and because of the active propulsion of the contractions of the uterine muscles. It will be recalled that with injection into the maternal blood of any colored particles the latter will appear in the amniotic fluid of the baby but never the reverse (Hinselmann).

The effect of any kind of an embolism depends on (1) the nature of the embolus; (2) the extent of tissue afflicted; (3) the rapidity with which the embolic obstruction is produced; and (4) the organ involved. The obstruction of a small branch of the pulmonary artery may pass unnoticed whereas death will follow immediately when one of the main branches of the artery is involved. Furthermore, the extent of the lesion caused by an embolus will depend on the type of blood supply of the organ involved. In an organ with abundant collateral circulation the damage resulting from the embolus may be negligible. Organs such as the lungs or liver have a double blood supply and an obstruction of a small vessel will cause little or no effect with only the blockage of a greater branch doing irreparable damage (Boyd[3]). The uterine embolism intra partum from any cause has been considered possible only when there are thrombotic veins in the parametrium or open veins in the region of a tear in the parametrium or, in cases of placenta previa, where large veins have been torn or in a rupture of the uterus. Intrauterine manipulation without tears may cause only air embolisms which are not usually fatal (Hinselmann).

Steiner and Lushbaugh confirm that there are other embolic phenomena than the amniotic but claim that these other emboli are not so severe, e.g., blood clot, placental tissue, or decidual tissue, with which claim this writer wholeheartedly subscribes.

The next two cases (Cases 9 and 10) were reported by these same investigators[2] in the following year (March, 1942).

CASE 9.—A 35-year-old primipara, at the Illinois Central Hospital, Chicago, died seven days after delivery of a stillborn full-term infant. Labor lasted four hours with the

second stage of labor continuing for 20 minutes only and the third stage lasting only 10 minutes. The patient developed severe pain in the right shoulder, became listless, and the abdomen became very sensitive. After the delivery the pain still continued and the patient began to vomit. She received several transfusions. The abdomen enlarged and kept growing. A tender mass appeared in the right lower quadrant. She developed convulsions and died. Postmortem findings: The mother had 400 c.c. of bloody fluid and dark bloody clots in the peritoneal cavity. A 3 cm. long laceration through the left uterine isthmus was noted which extended through the uterine plexus. The authors state that there were no gross pathological changes except that the organs were very pale. Microscopically, the small arteries and arterioles and capillaries of the lungs were occluded by a structure resembling mucin and by crescent squamaelike bodies. This material was infiltrated by large mononuclear macrophage-like leukocytes of all kinds. Giant cells were among them with these resembling lanugo hair. The uterine tear had thrombocytic veins and hemorrhage in the areolar tissue. The capillaries and arteries of the omentum were surrounded by decidua cells.

No comment is necessary inasmuch as the pathologist reported as follows: massive intraperitoneal hemorrhage from rupture of the uterus. Perhaps the life of the patient could have been saved had the obstetrician acted energetically following the forceps operation when he first observed the growing mass.

CASE 10.—A 38-year-old para ii, gravida iv, was admitted to the Chicago Lying-in Hospital because of hypertension. The urine had traces of albumin. Medical induction of labor was without success. Two days after admission painless bleeding occurred. A diagnosis of anterior placenta previa followed and a laparotrachelotomy was performed under local anesthesia. The placenta had to be pierced and the fetus delivered by version and extraction. After the operation, no pulse was obtainable and the patient became very pallid. She received two transfusions of blood, the uterus was packed, but she continued to bleed. She died 3½ hours later. In spite of the clinical diagnosis, placenta previa totalis, toxemia, and hemorrhage, the authors sought further for the cause of death. When the capillaries and arterioles of the lungs were found to be filled with mucus and squamous cells, they had in their estimation sufficient evidence to support the theory of amniotic embolus as the death-causing factor.

These two additional cases suggest to this writer how a fixed idea can confuse the issue and divert the surgeon from proper action.

CASE 11.—A 40-year-old woman was admitted to the Rumford Community Hospital, Maine,[4] with a diagnosis of pregnancy at term. The membranes ruptured four hours before admission and active labor began seven hours after the rupture and lasted three hours. A dead baby was delivered spontaneously under ether anesthesia. While on the delivery table, the patient complained of severe pain in the right hip, radiating down the right thigh. Two hours after delivery the patient began to cough and wheeze. The cough was dry and nonproductive. She vomited bile-colored fluid, then developed cyanosis, respiration became more difficult, and she died. At autopsy, the lungs were heavy and wet, large amounts of white frothy fluid were expressed from the cut surface; the major pulmonary vessels revealed, however, no gross evidence of embolism. The pulmonary arterioles were massively distended with plugs of epithelial squamae, mucus, meconium, and numerous leukocytes and lymphocytes.

Comment.—No statement about the bronchial tree was found. The appearance of the lungs, the richness of frothy fluid, and the delivery only three hours after admission under anesthesia and with a full stomach make plausible the conjecture that the sudden death in this case was due to inspiration of the contents of the stomach into the lungs.

CASE 12.—A 33-year-old, white woman, para i, gravida ii, was admitted to St. Luke's Hospital, Cleveland,[5] with ruptured membranes and slight bleeding. Since no labor developed, a castor oil induction at 10 P.M. was attempted. Sudden bleeding developed at 2 A.M. the next morning. Between March 17 and 18 the temperature had risen gradually to 40.9° C. (107° F.). Systolic murmurs all over the heart were audible. Seventy-two hours

after the rupture of the membranes, a spontaneous delivery of a stillborn baby occurred. The placenta had a very bad smell. The patient died one hour later bleeding from the mouth. At autopsy, thrombi were found in the small capillaries of the lungs.

I would comment simply that death was caused by acute sepsis.

CASE 13.—A 25-year-old white woman, secundipara, was admitted to St. Joseph's Hospital, Pittsburgh, Pennsylvania.[6] Eleven hours previous to admission, a bloody vaginal discharge appeared followed in two hours by the first labor pains 15 minutes apart. About nine hours later the membranes ruptured spontaneously. Uterine contractions had been tetanoid. One hour later the cervix was fully dilated. The patient became chilled and died on the delivery table. Before she died she had convulsions, went into coma, became pulseless, and there was conjugate deviation of the eyes to the right. Blood pressure fell to 30/00. The baby, dead, was delivered by version and extraction during the last 5 minutes. Microscopically, the arteries and most of the arterioles of the lungs were occluded by a mixture of leukocytes, monocytes, and granular debris.

Considering the course of the premortem symptoms a cerebral pathology is plausible.

CASE 14.—A 42-year-old white woman, tertipara, came to the same hospital[6] as above with the cervix dilated to 2 cm. Artificial rupture of the membranes was performed and a large amount of amniotic fluid drained off. But no labor developed in spite of 6 injections of Pitocin. Thirty-four hours after admission tetanoid contractions set in. Three hours later a forceps delivery of a stillborn baby under ether anesthesia was performed. About an hour later the patient died. At autopsy, on opening the abdomen, about 200 c.c. of blood were found. There was diffuse extravasation into the preperitoneal tissues of the anterior abdominal wall below the umbilicus. There was also ecchymosis in the right broad ligament of the uterus involving also the right tube and ovary. This ecchymosis was visible in the mesentery of the ileum and cecum. Microscopically, the pulmonary arterioles and the alveolar capillaries were bloodless but were occluded by polymorphonuclear leukocytes and a small amount of granular debris. The liver cells were swollen and occasional small portal veins showed cellular contents as in the arterioles.

In my opinion, death was due to hemorrhage and shock caused by the prolonged and protracted labor.

CASE 15.—A 35-year-old quintipara was admitted to the same obstetrical service at St. Joseph's Hospital (as the two preceding cases) in active labor one month before term.[6] The first labor pains began about two hours before admission and were accompanied by a slight bloody show. Temperature, pulse rate, and respiratory rate were normal. The membranes ruptured spontaneously and it was noted at this time that the amniotic fluid contained fresh blood. Baby and placenta were normally delivered. Twenty minutes following delivery, during which the patient was alert and communicative, there was an emesis of green-tinted fluid. Five minutes later this was followed by stupor and coldness and clamminess of the skin. The blood pressure was 40/20. Within 15 minutes a severe hemorrhage from the uterus followed. Despite antishock treatment, death occurred one hour after the onset of symptoms listed. Autopsy found the uterus normal for its puerperal state. The placenta and membranes showed no abnormality. There was, however, extensive thrombosis of veins of the broad ligaments. These thrombi were soft, of currant-jelly type, and not attached to the vessel wall. Elsewhere the blood was thin and no clots had formed. The right auricle of the heart was dilated but the lungs were dry and spongy. Microscopically, there were extensive vascular occlusions beginning with the medium-sized pulmonary arteries and extending down to the alveolar capillaries. The lumina of these vessels were filled with a mixture of loosely packed leukocytes and granular material. Longitudinally cut hair shafts were found. There was no pulmonary edema. The liver was anemic. Thrombotic veins from the broad ligament showed no abnormality of the vessel wall. The thrombi, it is stated, were of recent origin and showed no organization (how quick could such come about!) and no attachment to the endothelium.

There is no doubt in my mind but that this patient also was a victim of hemorrhage and shock. The loose thrombi in the veins suggest, if anything, a blood clot embolism.

CASE 16.—A 25-year-old, gravida ii, para ii, was admitted to the Chestnut Hill Hospital, Philadelphia,[7] on Jan. 6, 1947, at 1:00 A.M., slightly past term. She had had a twin pregnancy in 1944, the second child being delivered by a difficult version and breech extraction. Membranes ruptured spontaneously at 8:00 A.M. the same day. Labor proceeded uneventfully until 9:50 A.M., at which time a rectal examination revealed a face presentation with almost complete dilatation of the cervix. While preparations were being made for the delivery, the patient suddenly became cyanotic, took several convulsive gasps, and ceased to breathe. At autopsy, the cervix was found thinned out, dilated, and completely effaced. On the right side, 2 to 3 cm. above the cervical lip, there was a ragged tear 10 to 15 mm. across. Considerable free exudates flowed from this opening after removal of the fetus. The opening led almost directly into the broad ligament which was enormously swollen and boggy with fluid. This swelling extended into the adjacent retroperitoneal space and up the kidney and reached almost to the liver. All of these tissues were almost translucent with fluid, the total amount of which present appeared to be 500 c.c. Microscopically, the presence of numerous intra-alveolar macrophages laden with yellowish brown and black pigment granules was noted. These resembled heart failure cells very closely. In the capillaries and arterioles there were bits of foreign material of uncertain nature. Watkins,[7] in correlating the pathologic findings, stressed that the amount of particulate matter observed in the lungs was relatively small, and in itself was probably not sufficient to cause death.

Dr. J. Robert Willson, in discussing this case, referred to his own lack of conviction regarding cases in the literature reported as deaths from amniotic fluid emboli. Quoting from his remarks: "Amniotic fluid embolus is going to be a good out in the future for sudden deaths during delivery, and I think before making the diagnosis we should consider and eliminate all the other causes of sudden death which may occur during labor." This quite neatly expresses the author's own reservations in the matter. As to this particular case, it is my opinion that the tear of the uterus occurred with probable damage to the ureter and was accompanied by retroperitoneal extravasation extending from the kidney to the bladder.

CASES 17 and 18.—In the discussion following the Watkins presentation of a case (cf. Case 16), Dr. William R. Nicholson cites two cases, not proved by postmortem examination, on which he had made the provisional diagnosis of amniotic emboli. One patient was a multipara who had been perfectly normal during the pregnancy went into labor early in the morning and before he, Dr. Nicholson, reached the hospital, was found dead by nurses. He reported that a necropsy was not obtainable. The other patient, also a multipara, who had been in normal labor for a short time, was examined by him and found to have a prolapse of the knuckle of the cord. She was immediately anesthetized "and the easiest version that I ever did was performed." During this procedure she suddenly became blanched and, in spite of stimulation, she died seven hours later. No postmortem was obtainable.

We would simply observe that a diagnosis on any patient cannot be made without accurate postmortem examination and unless the microscopic pulmonary pathology s demonstrated.

CASE 19.—A 32-year-old white woman, para iv, was admitted to the University Hospital, Minneapolis,[8] with a brownish vaginal discharge. Sixteen hours prior to admission she experienced a sudden loss of blood from the vagina. She was packed to control the bleeding and sent to the hospital with the diagnosis of placenta previa. Sixty hours after admission a moderate amount of fresh bleeding occurred. A cesarean section was performed. The infant died in five minutes. Following the delivery, the mother complained of rather severe pain in the abdomen and was given Pentothal intravenously. Five minutes after induction of the Pentothal the patient died. At autopsy, the findings were as follows: no pulmonary thrombi, no air embolism, no lung abnormality, no infarction, no edema. Microscopically, the small arteries, arterioles, and capillaries of the lung were filled with epithelial cells and protein material and leukocytes. Otherwise the parenchyma was normal.

A Porro operation, at admission, very probably might have saved her life.

CASE 20.—A 31-year-old white primipara was admitted to a local hospital (Minneapolis) on March 20, 1941, in labor.[8] The pregnancy had been uneventful until three hours after onset of labor. At that time uterine bleeding occurred which persisted until delivery. Five hours after admission she was delivered by low forceps. Bleeding followed the delivery which was not checked by expression of the placenta. The uterus was packed with gauze. A laparotomy was tried but the patient died. At autopsy, the peritoneal cavity contained about 1 L. of serous fluid. A laceration of the uterus measuring 8 cm. in length and 12 mm. in depth began at the internal os and extended through the thickness of the lateral wall of the uterus. In the broad ligament opposite this laceration there was a large hematoma. A smaller laceration was found on the opposite side of the uterus, arising at the internal os and extending upward 3 cm. Microscopically, sections of the lungs showed a mucinous material filling the small arteries. Section of the uterus showed considerable necrosis of the myometrium beneath the tear.

Undiagnosed rupture of the uterus spells certain death and there is no need of further comment.

CASE 21.—A 23-year-old white primipara had a bad pregnancy.[9] There were nausea and vomiting and a loss of 10 pounds in weight during the first two months. The expected date of delivery was Dec. 3, 1948, but on December 1 she began to show a bloody vaginal discharge consisting of both black and red blood. The patient did not go into labor but on December 8 she was admitted to the Nebraska Methodist Hospital, Omaha, where she was given quinine followed by castor oil and a hot enema. The fetal membranes were ruptured the same day and during the procedure soft tissue resembling placenta had to be penetrated. The following day at about 9:00 A.M. strong uterine contractions occurred but the cervix would not dilate. Two hours later because of marked fetal distress a modified Scanzoni maneuver was carried out to deliver a stillborn male fetus from a right occiput posterior position. Atony of the uterus was marked and there was no attempt to deliver the placenta as the patient began to gasp and died quickly. The gross examination revealed that the placenta was attached laterally on the left, the inferior margin reaching the level of the cervix. It was detached at this point over an area which was approximately 20 to 25 per cent that of the placenta. There was a laceration caused by the forceps. Microscopically, the precapillary arterioles were filled with amniotic fluid debris but the larger vessels showed no accumulations. One arteriole contained a lanugo hair.

In my opinion death resulted from hemorrhage and shock. Protracted labor, detachment of the placenta with atonia and bleeding present grave hazards. Massaging of the fundus through the abdomen, in my opinion, did not help the situation. Manual removal of the placenta, tamponade with transfusion and eventual extirpation of the uterus might possibly have brought about a happier result.

CASE 22.—A 40-year-old woman, gravida iv, para ii, past term, received quinine and Pituitrin to induce labor shortly after entering the hospital on July 1, 1948, in early afternoon.[11] Irregular contractions began July 2, 12:50 A.M., with the membranes rupturing at 2:15 A.M. There was a large amount of dark, bloody discharge. At 2:45 A.M. the patient had sudden twitchings of the arms and became very cyanotic. Death occurred at 3:00 A.M., 13 hours after admission to the hospital, slightly more than two hours after onset of labor. At 3:05 A.M., a postmortem midforceps operation was done, with the extraction of a living male infant. At autopsy, the lung findings were as follows: grossly, there was no crepitation, no consolidation, no edema, no hemorrhage, and no air bubbles. Microscopic sections of lung tissue revealed the lumen of many arterioles and capillaries filled with epithelial squamae, mucus, amorphous debris, and blood cells.

Nothing was found descriptive of other internal organs. This, it is felt, constitutes a serious omission.

CASE 23.—A 28-year-old gravida ii, para i, was well until ten minutes before admission to the hospital when the membranes ruptured.[10] She fainted, collapsed with frothing at the mouth and cyanosis. She was brought to the hospital dead by her husband. A 7 pound, 4½ ounce female infant was delivered alive by cesarean section but died 21 minutes later. Microscopically, there was marked dilatation of arterioles and capillaries. The arterioles

contained amorphous debris that stained specifically with sudan IV for fat. There was no evidence of hemorrhage within the abdomen or externally. Careful examination of the uterine vessels in the musculature around the cervix and in the corpus failed to reveal particulate components of the amniotic fluid. Point of rupture of the membranes was at the external os but the site of entrance of the amniotic fluid was not searched for.

No other significant findings were noted and, in this writer's view, this may have been a case of chronic heart disease.

CASE 24.—A 28-year-old gravida iv, para iii, was admitted to St. Joseph's Infirmary, Houston, Texas, at 6:45 A.M. on Aug. 21, 1949.[12] At 8:40 A.M. the cervix was fully dilated. The patient was taken to the delivery room at 8:43 A.M. when she vomited one-half cupful of green liquid material and became cyanotic. She was coughing occasionally. The delivery was terminated by low forceps (a stillborn infant). Following delivery, the patient continued cyanotic, the pulse remained above 160 but the blood pressure failed to rise. Death followed. Findings of the postmortem examination: Each pleural cavity contained approximately 200 c.c. of light amber fluid. The lungs contained much frothy fluid which also was present within the bronchi. No thrombi were found in the pulmonary artery or its branches. Microscopically, the lungs showed elements of amniotic fluid in many of the capillaries and arterioles. Many of the alveolar spaces were filled with edema fluid.

This, in our judgment, points to a circulatory collapse because of the transudates in the lungs and pleural cavity. An amniotic embolus could not so quickly produce these transudates in the pleura.

CASE 25.—A 33-year-old Negro woman, para vi, gravida vii, was admitted to Lynchburg General Hospital, Virginia, in early active labor at term.[13] Previous deliveries had been normal. Blood pressure was normal but there was questionable rupture of membranes. An enema was given with good results and mild, irregular pains continued. The urine showed a trace of albumin. A long protracted labor followed. On the morning of the eighth day one hour following an enema with good results, the patient was suddenly seized with sharp pain in the abdomen and within two minutes was dead. A postmortem cesarean section was done ten minutes later and a living female child in poor condition was delivered. She lived about 48 hours. Gross autopsy findings: The right chambers of the heart were distended as were also the pulmonary arteries and venae cavae. The pulmonary arteries exhibited no emboli and the bronchial tree was clear. The liver was flabby and the parenchyma bulged on section. The adrenals and kidneys were congested. The left broad ligament was prominent, markedly edematous, and contained blood. The edema extended throughout the parametrial tissues and upward into the left gutter. Dissection revealed a longitudinal tear 10 cm. long in the left wall of the uterus. After the removal of the fetus and placenta, a hemorrhagic tear 4 cm. long was found on the right posterior wall extending a short distance into the myometrium. Microscopically, sections from the area of the uterine tear showed intravascular clotting with organization and a layer of necrotic debris containing leukocytes and evidence of fibroblastic repair. Sections of lungs showed some terminal branches of the pulmonary artery packed with blood, others partly or completely filled with mucinous material similar to that found in the uterine sections.

Here we are considering a case of labor which extended into the eighth day. And we are at once reminded of Döderlein's dictum to the effect that the obstetrician should never allow the sun to set twice on anyone's labor. It is always wiser to find out why labor does not progress than to search later for the cause of death. This uterine rupture very likely was caused by the discrepancy between the size of the baby's head and the pelvis. The incomplete but protracted rupture of the uterus developed without manifest shock because the blood or hemorrhage was blocked.

Discussion

My analysis of these twenty-five cases of obstetrical deaths reported as resulting from amniotic emboli may be summed up by the following division into four groupings: (a) seven patients afflicted with internal diseases; (b) five

patients with intrapartum or postpartum hemorrhage; (c) eight patients with definite rupture of the uterus; and (d) five cases without sufficient findings either to deny or affirm the supposition that the fatality was caused by an amniotic embolus. In short, twenty cases had a definite cause of sudden death other than that attributed, namely, amniotic emboli, and five cases we would not classify one way or another because of the lack of significant autopsy findings. We refuse to recognize the microscopic findings as reported in all cases because of the following factors: During pregnancy the capillaries all over the body and not alone in the lungs undergo changes from slight lability toward paresis. This causes a disturbance in the exchange of fluids and other matter between elements in and out of the capillaries. The blood remains ten times as long in the capillaries of the pregnant woman as in the capillaries of the nonpregnant. The endothelium of the capillary wall will show a greater permeability during pregnancy which is caused by a loosening of the endothelial cells. As a result, exudation or even bleeding per diapededis is more likely to occur. This will explain in large part the postmortem findings in the lungs. As stated before, and I would repeat it again, various decidual and placental cells may appear in the lung capillaries without doing any damage to the body.

As to the toxicity of the amniotic fluid and its contents, e.g., meconium, this writer cannot accept as convincing proof the experiment by one of the authors who by injecting concentrated meconium into the veins of a rabbit produced emboli in the lungs. It would seem perfectly obvious that there is a difference between the amniotic fluid which tends to flow downward and a concentrated meconium substance which has been shot under pressure directly into the vein of a rabbit.

The writer worked for many years in the obstetrical clinic of the Frauen Hospiz, Vienna, where the uterine douche after manual removal of the placenta has been a routine procedure. The fluid put into the uterine cavity consisted of a one-third saline solution, one-third alcohol, and one-third tincture of iodine solution. This very warm solution passes through a fully dilated cervix into the uterine cavity causing uterine contractions. This is done only in cases of atonic or other kinds of postpartum hemorrhage and only when the uterine cavity is intact and where there is no tear in the parametrium. In hundreds of such cases, in my experience, an embolus has never occurred!

I maintain, in concluding, that the chief dangers in obstetrics still remain shock and hemorrhage and rupture of the uterus. The anticipation, evaluation, and prevention of complications continue to be the most priceless attributes of good obstetrical practice.

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22 Ingraham Place

THE CYTOLOGIC APPROACH TO UTERINE CARCINOMA: DETECTION, DIAGNOSIS, AND THERAPY

E. L. HECHT, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, the Post-Graduate Medical School, New York University-Bellevue Medical Center)

TWENTY-FIVE years ago, the outlook for curing uterine cancer was almost hopeless.[1, 2, 3] Today, because of significant advances in the recognition and treatment of this disease, the possibility of a high cure rate is relatively good.[4, 5, 6] At the present time the favorable chance for increasing this rate can be directly attributed to cytologic diagnostic methods. This paper proposes to discuss the cytologic method as a threefold approach to the problem of uterine cancer: (1) early detection of malignancy; (2) differential diagnosis; (3) guidance and control of therapeutic procedures.

Technique

At the University Hospital, the smear technique is included in every routine gynecological examination.

The desquamated cells are obtained in several ways: three different smears are taken from each patient, vaginal, cervical, and (since January, 1951) endometrial. The vaginal smear is obtained by aspirating secretion from the posterior fornix with a pipette attached to a rubber bulb. Patients are cautioned not to douche 24 hours prior to examination. The secretion obtained is expressed on a marked glass slide and immersed immediately in a fixative made of equal parts of ether and 95 per cent alcohol. Cervical smears are obtained either by aspirating the mucus directly from the cervical os, or by scraping the ecto-endocervical junction with a wooden spatula. The endometrial smear is taken by inserting a special cannula into the endometrial cavity, to which a syringe is attached. Gentle suction is applied and the aspirated material is spread on slides and fixed. The endometrial smear technique is a little-known innovation, concerning which a controlled study is currently in progress. An attempt is being made to correlate cytologic endometrial abnormalities (including endometrial cancer) with a history of abnormal bleeding during menarche and postmenopausally. Gratifying results have already been obtained. Not only have several cases of carcinoma been detected which were missed with the cervical and vaginal smears, but evidence of endometrial abnormalities such as endometrial hyperplasia, polyps, fibroids, and luteal phases of the endometrium has been uncovered.

The methods used in taking the smears are extremely simple and easily mastered, and are followed by the standard Papanicolaou staining technique, utilizing Harris' hematoxylin, OG 6, and EA 50.[7, 8, 9] This stain gives excellent nuclear detail which is extremely important in diagnosing malignant cells.

Carcinoma of the Cervix

The value of the vaginal smear in diagnosing carcinoma of the cervix is universally accepted today. Since 1945, its accuracy approaches 98 per cent.[10, 11, 12]

An exact histological diagnosis of squamous-cell carcinoma is not attempted. The classification includes two main groups: undifferentiated and differentiated malignant cells. The basis for distinction between the two groups is the presence or absence of distinct cellular borders. In undifferentiated cells, the cytoplasm is an indistinct background with absence of cell borders. Differentiated malignant cells have well-defined cytoplasm and fairly definite cellular borders (Figs. 1 and 2). The criteria for diagnosing malignancy are nuclear, however.

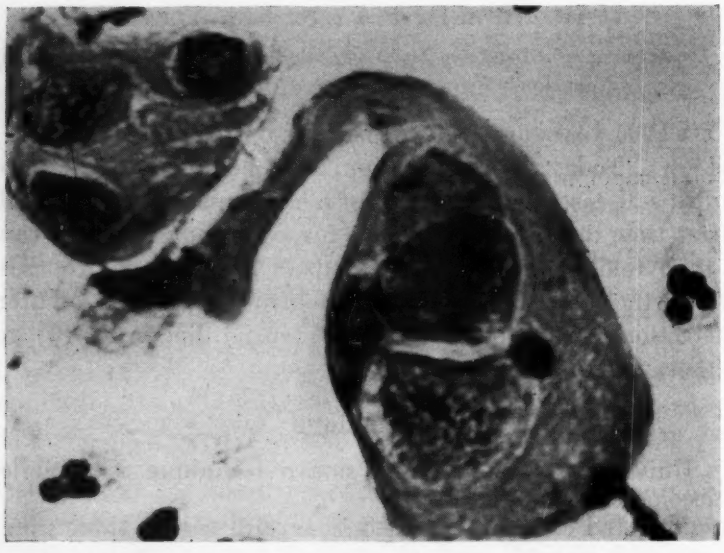

Fig. 1.—Squamous-cell carcinoma of the cervix showing a cluster of well-differentiated malignant cells in which the cytoplasmic cellular borders are clearly defined. Hyperchromatism, irregularity of the chromatin network, and variation in the size and shape of the nuclei are clearly evident. The typical "tadpole" shaped cell is clearly apparent.

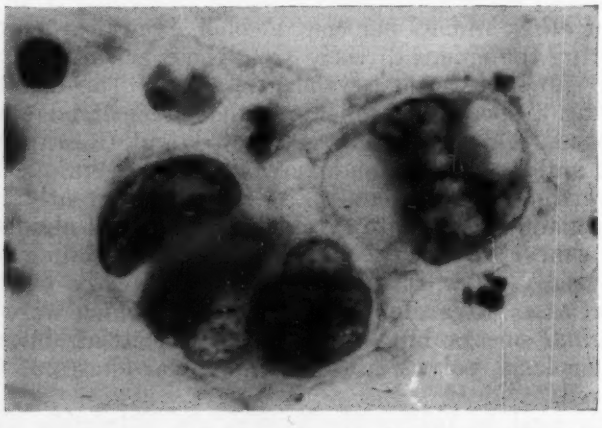

Fig. 2.—Squamous-cell carcinoma of the cervix showing well-differentiated malignant cells with vacuolization of the cytoplasm and marked nuclear atypicalism.

Listed in order of importance they are: (1) irregularity of chromatin network, (2) increase in chromatin content and (3) variation in the size and shape of the nucleus.

Differentiated malignant cells from squamous carcinoma are of 3 main types: (1) the fiber cell is a thin, elongated cell with a hyperchromatic,

elongated nucleus; (2) the so-called "tadpole" cell has, as the name implies, a "head" containing the deep-staining nucleus, and a "tail" of cytoplasm; (3) the most differentiated malignant cell shows the greatest degree of maturation. It resembles an inner layer basal cell, but the nucleus is hyperchromatic and abnormality is seen in the cytoplasmic-nuclear ratio (Fig. 3). Undifferentiated malignant cells from squamous carcinoma constitute the most common

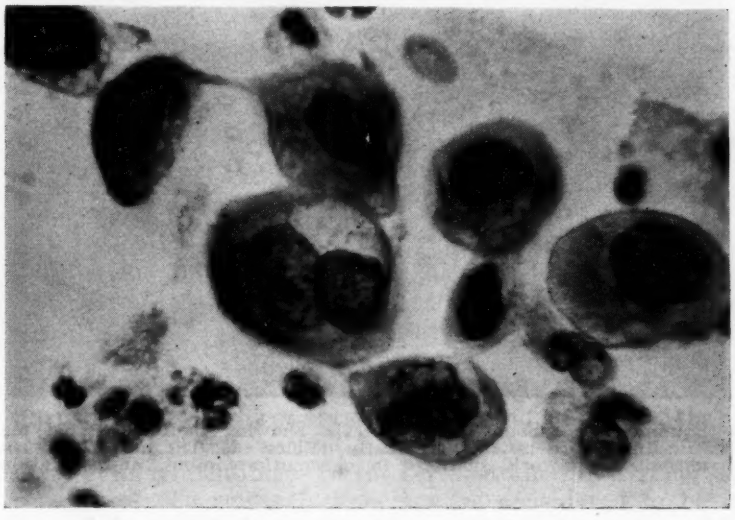

Fig. 3.—Highly differentiated squamous-cell carcinoma of the cervix showing a cluster of malignant cells resembling inner layer basal cells. The nuclei, however, are hyperchromatic and abnormalities in the cytoplasmic-nuclear ratio are apparent.

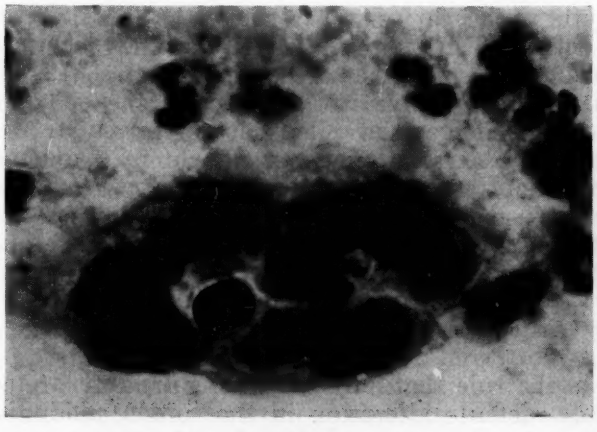

Fig. 4.—Undifferentiated squamous-cell carcinoma of the cervix showing a cluster of malignant nuclei with indistinct cytoplasmic borders. Numerous leukocytes and histiocytes are evident.

tumor cells encountered in vaginal smears (Figs. 4 and 5). A positive diagnosis can be made with greater assurance if groups of cells are encountered, than if only single cells are seen. Identification of single cells must be made upon nuclear structure. In groups, the additional criteria of variation in size and in shape give weight in the interpretation.

Smears from carcinoma of the cervix invariably contain numerous leukocytes, histiocytes, red blood cells, and frequently trichomonads. There is generally some degree of infection present.

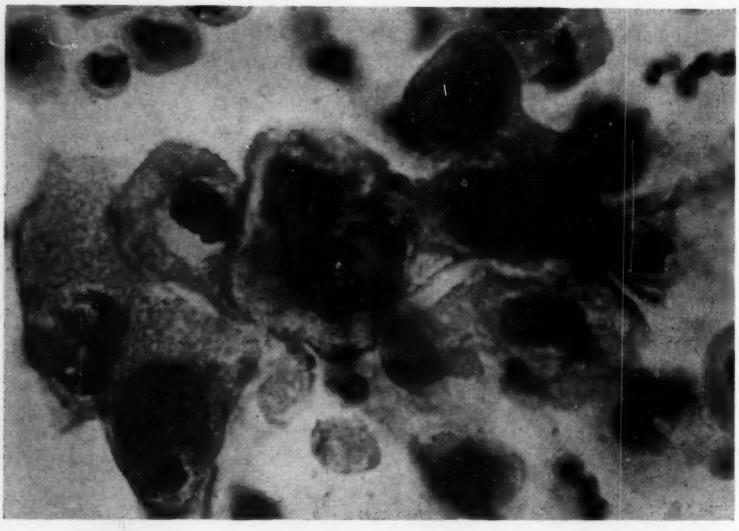

Fig. 5.—Squamous carcinoma of the cervix showing undifferentiated malignant cells. The cytoplasmic cellular borders are not clearly delineated. The nuclei show marked irregularity of the chromatin network, increase in chromatin content, and variation in size and shape.

Confusion Between Normal and Cancer Cells

Three types of normal cells, histiocytes, endometrial cells, and endocervical cells, are occasionally confused with undifferentiated malignant cells. (1) Histiocytes are indistinct in cellular outline and have a vesicular type of cytoplasm. Histiocytic nuclei vary more in shape than in size, whereas malignant nuclei vary in both size and shape. The typical histiocytic nucleus is bean-shaped and much smaller than that of malignant cells. (2) The second group of normal cells which may give rise to error is the endometrial cells. The chromatin in the fresh endometrial cell is smoothly granular; in the degenerated cell, it is pyknotic. Size variation is very slight in desquamated endometrial cells. In doubtful pictures, endometrial aspiration smears are of great value in eliminating the confusing degenerate forms. (3) Endocervical cells are often confused with tumor cells because the nuclei are characteristically large. In contrast to malignant nuclei, however, endocervical nuclei are vesicular, present no evidence of hyperchromatism, and show little variation is size and shape. In clumps, they display a regular arrangement resembling a "honeycomb" mosaic.

If we hold to the rule that only those cells are interpreted as positive for cancer which show definite alteration in the content and distribution of the chromatin, malignant cells may be identified with greater accuracy.

False Negatives.—In rare instances, smears from cases of squamous carcinoma may be read as negative: (1) when tumor cells are not shed (in rare tumors a greater cohesiveness between the cells will sometimes exist); (2) in the presence of severe secondary infection when even biopsies may fail to reveal carcinoma (advanced necrotic carcinoma will be clinically obvious); (3) misinterpretation of suspicious-looking cells. In the last case, methodical and intensive examinations by trained cytologists should be performed and smears repeated before a final diagnosis is made.

Biopsy.—A final diagnosis of squamous carcinoma of the cervix should always be corroborated with biopsy before surgical or radiotherapeutic procedures are instituted. The vaginal smear method is not intended to replace biopsy as a diagnostic method. There is no conflict between the two; the methods are complementary, and when utilized together will increase the accuracy of diagnosis. In a series of 181 cases of carcinoma of the cervix reported by Graham, Sturgis, and McGraw,[13] the initial biopsy was found correct in 91.2 per cent of the cases; the initial vaginal smear in 92.3 per cent. The combined methods were wrong in only 1.7 per cent of the cases.

In the earliest stages of malignancy, the vaginal smear has been found to be more accurate than biopsy. Normal and benign looking cervices may harbor an unsuspected malignancy, particularly carcinoma in situ. In 40 cases of carcinoma in situ reported by Graham, and Meigs,[11] the initial vaginal smear was correct in 87.5 per cent and the initial biopsy in 70 per cent. In 8 cases of carcinoma in situ studied at the Gynecological Cytology Laboratory of the University Hospital, New York University Post-Graduate Medical School, the vaginal smear was correct in 100 per cent. The biopsy was correct in only 70.5 per cent (6 cases). Even if one were to perform routine cervical biopsies, lesions not included in the biopsy site may be missed. Such cases, however, will be picked up cytologically, since a more even sampling of desquamated cells from the entire cervix is obtained. In the 112 cervical cancers studied at the Gynecological Cytology Laboratory of the University Hospital, 15, or 13.4 per cent, were unsuspected. Eight of these were carcinoma in situ, the earliest type of cervical cancer. In all 15 cases the only reason for performing the biopsy was the positive cytologic finding. In the series studied by Graham and Meigs,[11] 38 (8.5 per cent) of 432 cervical cancers were considered to be unsuspected. In 19 of these 38 cases, the reason for doing a biopsy was the positive cytologic report. In the remaining 19 cases, the symptoms were minimal. When routine cytologic examination is made, the danger of treating malignancy as simple erosion is minimized.

Adenocarcinoma of the Endometrium

Cytologically, adenocarcinoma of the endometrium does not show the marked cellular changes evident in carcinoma of the cervix.

Malignant cells from adenocarcinoma of the cervix exhibit the same characteristics as those from adenocarcinoma of the endometrium. The cells from adenocarcinoma of the endometrium are also classified in two groups, differentiated and undifferentated, the classification being based on the presence or absence of cellular borders. The differentiated carcinoma cell has: (1) a distinct cellular border which, however, is not quite as sharp as that in differentiated squamous carcinoma cells; (2) the cytoplasm of these cells is often vacuolated, occasionally pushing the nucleus to one side and thus presenting a "signet-ring" appearance; (3) the nuclei are larger, 3 to 8 times the size of a white blood cell, and eccentric rather than central in location; (4) the nucleochromatin presents the characteristics evident in all malignant cells, hyperchromatism and marked granularity of network (Figs. 6 and 7).

The undifferentiated adenocarcinoma cells have a tendency to occur in tight groups; the cellular borders are indistinct, and vacuolization of the cytoplasm, although apparent, is less marked than in the differentiated cells (Fig. 8). The nuclei present the characteristic features of malignant cells. It is difficult to identify undifferentiated adenocarcinoma cells as coming from the endometrium. Endometrial aspiration smears will undoubtedly obviate this difficulty. The clinical history and physical findings would also be of extreme value in determining the site of such undifferentiated malignant cells in the vaginal smear.

The cytologic diagnosis of adenocarcinoma of the endometrium using the vaginal and cervical smear technique has not been as satisfactory or as accurate as with squamous-cell carcinoma of the cervix.[11, 14, 15] This may be attributed to three possible reasons: (1) Extreme degeneration of the desquamated endometrial cells often takes place before they reach the vagina and posterior fornix.

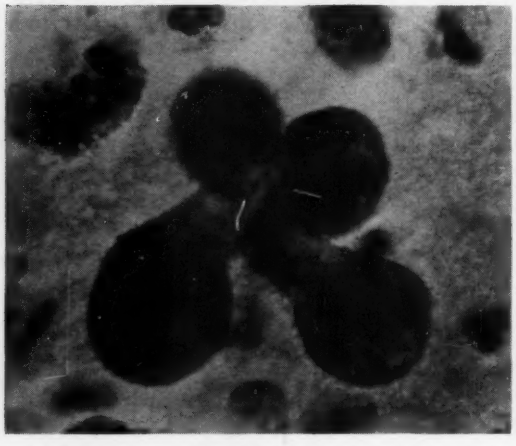

Fig. 6.

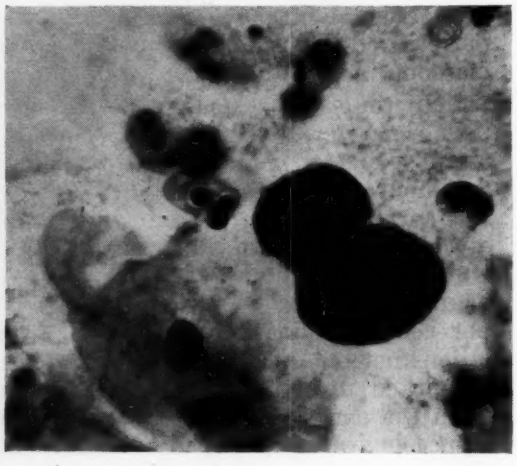

Fig. 7.

Fig. 6.—Adenocarcinoma of the endometrium showing a cluster of differentiated malignant cells. The cellular borders are distinct, and the cytoplasm slightly vacuolated. The nuclei show irregularity of the chromatin network and hyperchromatism.

Fig. 7.—Adenocarcinoma of the endometrium showing a cluster of differentiated malignant cells. The cells with the two nuclei appears to have just completed mitosis.

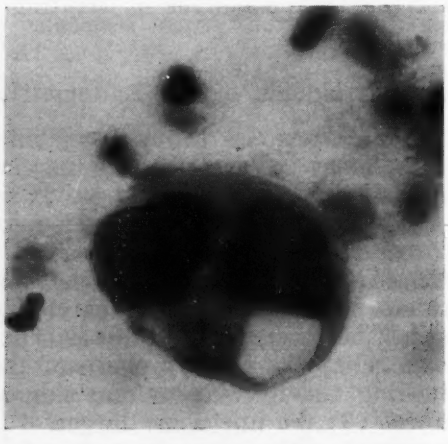

Fig. 8.—Adenocarcinoma of the endometrium showing a cluster of undifferentiated malignant cells with indistinct cytoplasmic borders, but marked vacuolization of the cytoplasm.

As a result, it is often difficult to evaluate abnormalities. (2) Some degree of cervical stenosis is commonly present in postmenopausal women. Consequently, few desquamated endometrial cells pass through the internal cervical os into the vagina. The number of cells presenting themselves on the vaginal smear may therefore be insufficient to make a diagnosis. (3) It may be difficult to make a cytologic differentiation between atypical endocervical cells and endometrial cells. These are the only two types of normal cells seen in the vaginal smear which cause such confusion. The ability to distinguish between enlarged endo-

cervical cells and malignant endometrial cells also depends entirely on the chromatin structure. Nuclei must show marked irregularity and clumping of chromatin material to be considered malignant. The nuclei of enlarged endocervical cells do not present such a pattern.

Desquamated cells from a hyperplastic endometrium may present a somewhat different picture. Considerable variation in size may be seen. They may occur in tight groups, occasionally with vacuolated cytoplasm. The nuclear structure, however, is perfectly benign. The vesicular finely granular pattern of the nucleochromatin is quite evident.

The use of the endometrial aspiration smear obviates some of the difficulties encountered in basing a diagnosis of endometrial adenocarcinoma on the vaginal-cervical smears alone. (1) The complicating and confusing endocervical cells in the diagnosis of endometrial cancer will be eliminated. (2) The degenerated forms of endometrial cells which at times are confused with carcinoma cells will also be largely eliminated as a source of error. With the endometrial aspiration smear, the nuclei are fresh and well preserved, facilitating accurate identification of abnormal nuclear structure. (3) The difficulty encountered in identifying undifferentiated malignant cells from squamous carcinoma of the cervix and adenocarcinoma of the endometrium will also be eliminated.

These three factors help explain why the accuracy of diagnosis of endometrial carcinoma has not been as striking as in carcinoma of the cervix. Some of the earliest statistical work revealed a 70 per cent[11] accuracy in diagnosis of endometrial carcinoma, a percentage corroborated by the author's own studies. Papanicolaou and Traut[8] failed to detect malignancy in 7 of 53 patients with carcinoma of the endometrium, giving an accuracy of 86.6 per cent, and 9.3 per cent false negative. With increasing experience, there is a steady diminution in the number of false negative smears in carcinoma of the endometrium. The use of the endometrial aspiration smear gives promise of the high degree of accuracy now obtained with carcinoma of the cervix. Having access to the endometrial cavity will also help eliminate the questioned reliability of a negative smear.

Radiation Therapy*

The vaginal smear as a guide to the effectiveness of treatment in cancer has proved itself empirically. It is an accurate indicator of the radiosensitivity of tumors, and a detector of malignant recurrence after radiotherapy and/or surgery.

Both normal and malignant vaginal cells are affected by exposure to either roentgen rays or radium emanations. The normal cells show: (1) an increase in the size of both cytoplasm and nucleus with no disturbance of the nucleocytoplasmic ratio; (2) marked vacuolization of the cytoplasm and occasionally of the nucleus; (3) the presence of bizarre forms.[16]

Normal basal cells are the first to show radiation effects (Fig. 9). After approximately one week of standard x-ray therapy (2,000 r) the staining reaction of the cytoplasm changes from acidophilic or basophilic color to yellowish-brown; aberrant forms begin to appear and the nuclei reveal degenerative changes (pyknosis and karyorrhexis). About the twelfth day, the basal cells increase three to four times their normal size; the nucleocytoplasmic ratio, however, is maintained. Brownish-yellow deposits which have been interpreted as glycogen appear in the cytoplasm. About the fifteenth day, marked vacuolization of the cytoplasm occurs. Multinucleated basal cells begin to appear. The appearance of "bizarre" forms is the final change to occur in basal cells.

*Much of the knowledge of the effect of radiation therapy on structural cell changes is based on the work done by R. M. Graham of the Vincent Memorial Hospital Laboratory of Boston, Mass.

An elongated, dumbbell or tadpole-shaped cytoplasm may appear. These cells may occasionally resemble differentiated malignant cells. The nucleochromatin is the significant feature, however. The malignant nucleus reveals hyperchromatism, irregularity, and clumping of the chromatin, whereas the normal irradiated nucleus is fairly granular.

Basal-cell radiation changes will occur only if the smear contained basal cells before radiation. If the patient is premenopausal, the radiation changes are seen first in the precornified cells, since few basal cells are normally present.

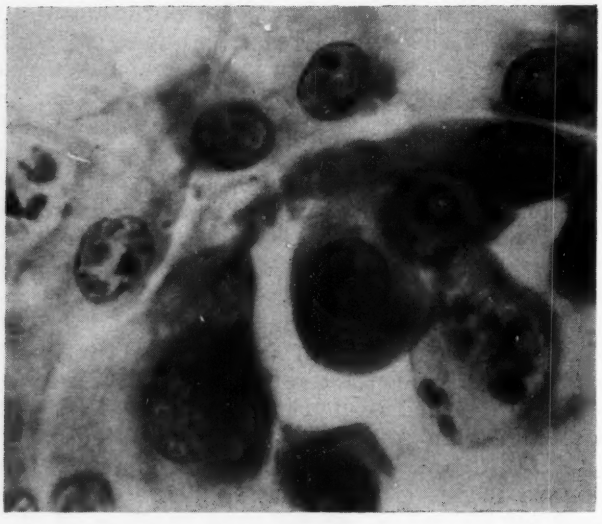

Fig. 9.—Radiation changes in normal basal cells showing enlargement of the cells with preservation of the nucleocytoplasmic ratio. Vacuolization of the cytoplasm and karyorrhexis of the nuclei are evident.

The precornified superficial cells begin to show the effects of radiation about the fifteenth day. The cell increases three to six times normal size, maintaining, however, its nuclear-cytoplasmic ratio. The nuclei undergo degenerative changes, showing evidence of pyknosis and fragmentation. When the nuclei begin to show evidence of degeneration, the cytoplasm also shows signs of radiation effect. Very fine fibrils appear in the cytoplasm, and marked vacuolization also takes place. Bizarre forms, not quite as striking as in basal cells, begin to make their appearance about the eighteenth day. The last change to occur in the precornified superficial cell is the appearance of polymorphonuclear leukocytes. This takes place about the twentieth day post radiation (Fig. 10).

The cornified superficial cells show the same radiation effects as the precornified cells except that the nuclei remain pyknotic and do not increase in size.

Malignant cells begin to show radiation effects 24 hours after the onset of treatment. The effects are similar to those seen in normal cells, except for the nucleus. There is an increase in the size of the cell (three to four times) and marked vacuolization of the cytoplasm. The nuclei increase tremendously in size and the malignant nuclear characteristics are accentuated. There is a relative increase in the irregularity, density, and clumping of the nucleochromatin (Fig. 11).

The irradiated differentiated squamous carcinoma cell often resembles the irradiated large "bizarre" normal cell. It is therefore unwise to make a diagnosis of recurrent carcinoma on the basis of irradiated differentiated cells. The diagnosis of persistent tumor or recurrence following radiation therapy should be made only when undifferentiated malignant cells are unmistakably seen.

Malignant cells usually disappear within 8 to 12 days following the onset of radiation therapy, but occasionally may persist 6 weeks or more. By the end of 3 months, however, most radiation changes in deep and superficial cells disappear. No malignant cells should be found at this time.

All the foregoing criteria have been developed through the utilization of the cytologic method. The vaginal smear is thus an invaluable aid in determining the prognosis of malignancy during radiation therapy. Normally the number of malignant cells decreases as the radiation-affected normal cells increase.

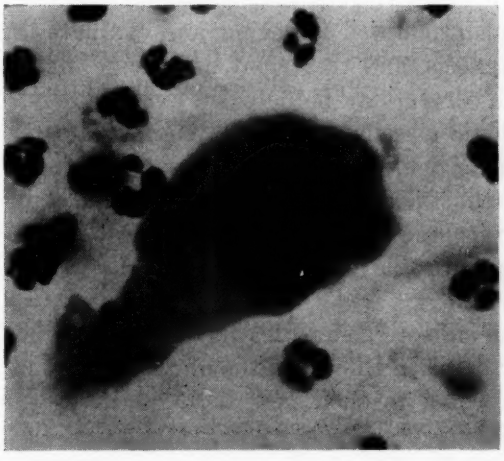

Fig. 10.—Radiation change in a precornified cell showing a pseudopodic "snakelike" configuration of the cell with marked disintegration of both cytoplasm and nucleus.

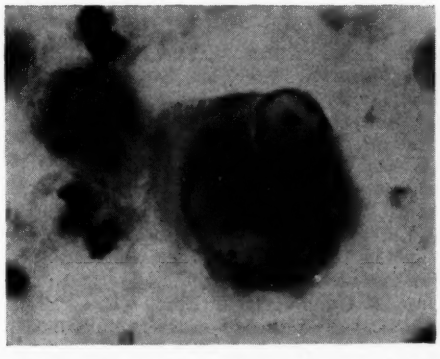

Fig. 11.—Radiation changes in malignant cells showing marked enlargement of the nuclei with distintegration of the nucleochromatin.

This is considered good response to radiation therapy. Response in the normal cells appears to be the most important factor in prognosis. If an immediate response is shown, the radiosensitivity of the tumor is clearly established. If the case is borderline and shows little or no response, better results may be obtained by re-evaluating the case after radiation and considering another therapeutic approach. The smear is therefore a practical follow-up procedure for patients undergoing radiation therapy.

The vaginal smear is also extremely useful in detecting postradiation recurrences. Following radiation, numerous adhesions may form at the apex of the vaginal vault. In addition, a contraction ring of scar tissue usually forms at the junction of the upper one-third and lower two-thirds of the vagina.

These factors may make it difficult to visualize and evaluate an irradiated cervix to determine whether a recurrence has taken place. To biopsy such a cervix may be a major procedure. In such instances the vaginal smear is an extremely valuable aid. The presence of undifferentiated malignant cells on the smear in a postradiation case may thus indicate a recurrence long before signs and symptoms become apparent. The study of postradiation smears is equally valuable in determining prognosis and in detecting early recurrence of malignancy.

Summary and Conclusions

1. This paper has attempted to review and evaluate the cytologic approach to the detection, diagnosis, and treatment of uterine malignancy.

2. Cancer of the cervix may be detected cytologically before clinical symptoms appear. Cytologic classification and diagnostic criteria for cancer of the cervix have been clearly defined. The accuracy of diagnosis is over 95 per cent.

3. Nuclear changes reflect the earliest abnormalities in cellular patterns.

4. The cytologic technique (vaginal and cervical smears) is simple, painless, and inexpensive, a practicable procedure in routine gynecological office examination.

5. The use of the endometrial aspiration smear, now being investigated, will reduce the chance of error in the diagnosis of cancer of the endometrium. This technique is also expected to shed new light on little-known endometrial abnormalities.

6. The cytologic study of postradiation smears serves as a guide in determining prognosis and detecting early recurrence in uterine cancer.

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THE USE OF APOMORPHINE WITH SCOPOLAMINE IN LABOR*

ROBERT R. WHITE, M.D., EAST ORANGE, N. J.

(From the Orange Memorial Hospital)

THE search for the best companion drug for scopolamine in obstetric amnesia-analgesia still continues. Recent studies lead us to believe that apomorphine is a satisfactory answer. The morphine component of popular "twilight sleep" was eventually rejected because of its unsatisfactory effect on the fetus. Scopolamine was recognized as a valuable factor of the combination in the early part of this century and, after due investigation, was found to be safe and constant in its amnesia-producing action. Today it is one of the most common components of combinations of drugs used for relief of pain in labor. Unfortunately at times therapeutic doses of scopolamine cause an undesirable cortical stimulation resulting in an excitement which is difficult to handle.[1] Many drugs have been used to combat this state of agitation and have not always been successful. Since 1939 Demerol in combination with scopolamine has seemed to prevent excitement quite satisfactorily. This drug, however, is not devoid of undesirable effects, one of which is a probable moderately depressive action on the fetal nervous system, resulting in an occasional sleepy baby or one exhibiting a delayed cyanosis.

Interest in the use of subemetic doses of apomorphine to control the excitement of scopolamine was aroused by the work of Hershenson and Brubaker[2] who studied 500 cases at the Boston Lying-in Hospital in 1946. They reported satisfactory control of excitement and, furthermore, a potentiating effect on the analgesic action of scopolamine. The safety of apomorphine when properly administered was emphasized.

The appearance of apomorphine in the field of analgesia was welcomed with great interest and some degree of surprise, in that an old drug having limited applications in the pharmacopeial dosage, and almost obsolete, could be used in labor. Its action was effective if it was given in very small dosages, much smaller than had commonly been considered useful. Consequently administration of apomorphine with scopolamine was undertaken at the Orange Memorial Hospital, Orange, N. J. Observations and tabulations of its effects were made as fully as possible in a suburban hospital which lacks many facilities desirable for complete scientific investigative study. Apomorphine-scopolamine analgesia was used routinely in 530 consecutive private cases of the author's. The combination was also used 174 times by 11 other physicians, total cases, 704. Observations reported here concern only the 530 above mentioned. Apomorphine was not used in eclampsia, heart disease with decompensation, or in premedication before elective cesarean section. The intent of

*Read, by invitation, before the New York Obstetrical Society, Dec. 11, 1951.

this series was to study the action of apomorphine in labor, and to report an additional number of cases exposed to it, thereby assisting in the evaluation of this drug. Since the effects of scopolamine are currently well known,[3] detailed discussion of its properties has been omitted in this paper. In no case in this series, however, was apomorphine used without scopolamine since the aim was to produce as complete amnesia as possible and to eliminate some of the objectionable features of scopolamine.

Since the discovery of apomorphine in 1845[4] and the announcement of its specific action in 1869[5] it has served as the only dependable central emetic. Early in this century it was found to be a safe and prompt hypnotic in coping with central nervous system disorders and alcoholic deliria.[5-12] H. H. Johnson,[13] who first used apomorphine with scopolamine in obstetrics, reported in 1925 that a small dose of $\frac{1}{50}$ grain "enhanced the action of scopolamine" and produced sedation similar to twilight sleep without danger to the fetus. Rovenstine[14] and Rovenstine and Hershey[15] have demonstrated the antagonistic effect of apomorphine to scopolamine, emphasizing the value of subemetic doses in the control of scopolamine excitement and emergence delirium. In 1947 Hershenson and Brubaker[2] reported a systematic and detailed study of 500 labors in which the combination of apomorphine and scopolamine was used to produce amnesia and analgesia in labor at the Boston Lying-in Hospital. They found some of the objectionable side effects of scopolamine to be obviated. Fifteen per cent of the patients showed moderate and 3.7 per cent showed marked excitement. No notable changes took place in the mother's condition or the progress of labor. There was "no demonstrable depressant effect on either full term or late premature infants." When labor was carried out under their regimen, and delivery took place without supplementary anesthesia, 100 per cent of the babies breathed and cried spontaneously and immediately. They state that the combination is safe, and "better from both maternal and fetal standpoints than other methods employed at this hospital." Later, in considering the basic principles of premedication and anesthesia in labor, Hershenson[16] found scopolamine to be the best amnesic available, and restated the action of apomorphine which intensified the analgesic action and neutralized the excitant effect of scopolamine. He observed a beneficial effect of apomorphine on upper respiratory infections present at the time of labor. A descriptive paragraph of findings of the Boston group appears in Lull and Hingson's book, *Control of Pain in Childbirth*.[17] Siehl,[18] in 1949, presented a series of 66 cases in which apomorphine-scopolamine was used in labor. He found it excellent in producing amnesia and analgesia, safe to use at any time in labor, and free of any untoward reaction on the mother or fetus.

Apomorphine hydrochloride is prepared by the extraction of a molecule of H_2O from morphine. The resulting structure and action differ radically from those of the parent alkaloid in that the depressant action of morphine is lost to a great degree while the stimulant action is retained. The most familiar action is the specific and direct stimulation of the so-called "vomiting center" in the medulla. Small doses have an expectorant and mild hypnotic effect of transient nature. Apomorphine does not cause narcosis, and no tolerance is acquired for it. Its fate is decomposition within the tissues.[5, 19, 20]

In this study interest centers on the hypnotic effect of this drug. Sleep follows emesis when the pharmacopeial dose ($\frac{1}{10}$ grain) is given. Injudicious use of this dosage in the treatment of acute alcoholism has caused cardiorespiratory collapse, thus earning an unsavory reputation for the drug. The small subemetic dose ($\frac{1}{100}$ – $\frac{1}{50}$ grain) seems to be devoid of danger to the

patient. A pleasant soporific state is quickly produced which lasts about 2 hours but in the absence of other drug effects this action is not uniform in its occurrence. When it is used in labor no apparent deleterious influence on the vital processes of the fetus is produced. While there is no detailed pharmacological research available on the subemetic dose of apomorphine in either the pregnant or nonpregnant individual, Snyder[21] assumes its passage through the placenta. He attributes the absence of effect on the fetus to the small doses used.

Procedure

The dosages used in this study were $\frac{1}{100}$ and $\frac{1}{50}$ grain intramuscularly or intravenously. These are obtained by dissolving a commercial tablet of $\frac{1}{10}$ grain apomorphine hydrochloride in 60 minims of sterile saline or water which is then kept in a sterile covered glass dish. Of this, 6 minims equal $\frac{1}{100}$ grain. Thus several doses may be given from the original solution of one tablet of $\frac{1}{10}$ grain apomorphine hydrochloride. All injections are made very slowly, as less nausea results from such administration. Intravenous injections should take 2 to 3 minutes. All the solutions used turn green before they are injected but no clinical evidence of untoward reaction of the drug has been noted in spite of pharmacopeial warning.[22] The action of the drug is fast, the first effects being evident in 2 to 5 minutes, and a maximal effect in about 20 minutes. The effects by the intravenous route occur in about half as much time as by the intramuscular.

In the study of the action of drugs in analgesia and amnesia a routine must be followed. After trial of dosages and intervals a routine similar to that of Hershenson was used for primiparas.

Table I. Sedation of Primiparas

1. For psychic sedation: Seconal, 3 grains, given preferably by rectum after admission enema	
2. For analgesia and amnesia:	
A. Apomorphine gr. $\frac{1}{100}$ Scopolamine gr. $\frac{1}{100}$	Given intramuscularly when patient begins to mind her pains and progress is being made
B. Apomorphine gr. $\frac{1}{50}$ Scopolamine gr. $\frac{1}{150}$	Given intramuscularly ¾ hour later
C. Apomorphine gr. $\frac{1}{50}$ Scopolamine gr. $\frac{1}{150}$	Given intramuscularly when needed after B and every 2 hours thereafter

A modification of this routine was used for multiparas or for fast primiparas when more rapid sedation was desired.

Table II. Sedation of Multiparas

1. For psychic sedation: Seconal, 3 grains, per rectum after admission enema	
2. For analgesia and amnesia:	
A. Apomorphine gr. $\frac{1}{100}$ Scopolamine gr. $\frac{1}{100}$	Given intramuscularly when minding pains
B. Apomorphine gr. $\frac{1}{50}$	Given intramuscularly 30 minutes later
C. Apomorphine gr. $\frac{1}{50}$ Scopolamine gr. $\frac{1}{200}$	Given intramuscularly 30 minutes after B and every 2 hours thereafter

In practice variation of the routines necessarily occurred due to differences in reactions of patients. It is obvious that systematic routines and observations are essential for the proper evaluation of drugs; but as skill and proficiency are gained in the employment of apomorphine and scopolamine individualized medication has been found to produce the best results.

Further instructions concerning apomorphine were used to supplement these routines:

1. Interval doses of apomorphine, gr. $\frac{1}{100}$ or $\frac{1}{50}$, may be given ad lib. either to control excitement or to strengthen the sedative action of scopolamine, but not more often than every 15 minutes.
2. In case rapidity of action is required either drug, singly or in combination, may be administered intravenously, slowly, taking 2 to 3 minutes for the injection.
3. Apomorphine or any portion of these routines may be used following or in conjunction with any other system of analgesia which already may have been started.
4. These drugs are not to be used in the presence of oxygen want due to heart disease, shock, respiratory obstruction, or pulmonary edema associated with eclampsia. They are also dangerous if esophageal lesions exist.

Comment

In early labor the administration of 3 grains of Seconal by rectum allays psychic apprehension and promotes a smoother induction of analgesia. If the sensorium has been slightly dulled by a barbiturate the stimulation of nausea and vomiting is less prominent. The first apomorphine-scopolamine injection is made when the contractions become uncomfortable. The patient is then asked to rest, relax, and breathe deeply during contractions. She is urged to think specifically of lying still, obeying instructions, and of attempting to go to sleep. A final appraisal of the psychological status of the patient at this point and her reaction to the actual onset of labor is important in guiding one with regard to the amount and frequency of scopolamine dosage. The first injection produces a feeling of giddiness and drowsiness and the cooperative patient will state after 10 to 15 minutes that she feels much relieved. Emesis, if it occurs, usually comes within 5 minutes and quickly passes off. The patient then sinks into a light slumber but may awaken with each contraction. After the second injection she sleeps more deeply but still responds to questioning. After the third injection she sleeps steadily and stirs with contractions, obeys commands, but does not converse intelligently. Scopolamine may be increased or decreased according to the physical size or mental state of the patient, or be omitted in subsequent doses if excitement seems too readily induced. In order to control excitement or to strengthen the analgesia of scopolamine, interval doses of apomorphine may be given as often as every 15 to 20 minutes until the desired effect is attained. If rapidity of action is desired, apomorphine with or without scopolamine should be given intravenously. Within 2 to 3 minutes the effect will be evident. A long labor may be continued with little complaint from the patient when the maintenance dosage is repeated every two hours. Those patients who have had three or more injections form the group in which the method is most satisfactory, for when questioned the following day they give evidence of complete amnesia. The patient having a rapid hard labor with only one or two injections will have islands of memory, will feel that the experience was not terrific, and that the analgesia, while not complete, was satisfactory.

During the second stage of labor the voluntary muscles are used automatically resulting in a spontaneous delivery in most cases. This is a striking feature allowed by this drug combination which definitely lowers the incidence of operative interference. Forceps were used only for definite indications and less frequently than with some other methods of analgesia. Spontaneous breech delivery is definitely favored by this method of premedication.

TABLE III. TYPE OF DELIVERY

	NUMBER	PER CENT
Spontaneous	402	76.00
Forceps plus aftercoming head	121	21.25
Breech	7	2.75
Total	530	100.00

The total forceps incidence at Orange Memorial Hospital during the time of this study averaged 35 per cent.

Apomorphine-scopolamine analgesia prepares the patient particularly well for conduction anesthesia (Tables IV and V).

Since a large proportion of patients have an active normal second stage with this method of premedication the anesthesia should be adapted to this fact. A definite attempt was made in this study to utilize fully the natural expulsive forces; consequently, spinal anesthesia was used as little as possible (saddle block, 9 cases, or 3.2 per cent). Over one-half of the patients received some form of local anesthesia. Also inhalation agents were used sparingly.

TABLE IV. ANESTHESIA AFTER APOMORPHINE-SCOPOLAMINE

TYPE	NUMBER	PER CENT
Conduction	281	53.10
Inhalation	166	32.85
Inhalation plus local	29	3.55
None	54	10.50
Total	530	100.00

These included cyclopropane, nitrous oxide-oxygen alone or in combination with ether, open ether, and chloroform. The latter was used only for emergency anesthesia for very rapid expulsive delivery. Inhalation was used in 32.85 per cent of the total series: 50 per cent of deliveries in the first 243 cases, but only 15.7 per cent in the following 287 cases. Thus, with experience and skill in timing and increased use of the intravenous route of administration of apomorphine, spinal and inhalation anesthesia was much reduced.

TABLE V. CONDUCTION ANESTHESIA

TYPE	NUMBER	PER CENT
Pudendal block	174	61.95
Vulval block	75	26.65
Perineal infiltration	23	8.20
Saddle block	9	3.20
Total	281	100.00

A very interesting feature is that no anesthesia at all was needed for delivery in 10.5 per cent of the patients. The baby was expelled, and an episiotomy, if necessary, was done and repaired without undue restlessness. Amnesia was complete in these women. The patient who has been quiet all through labor but becomes restless in the second stage can be controlled by successive doses of apomorphine if time allows before actual delivery. Occasionally, light inhalation anesthesia was given those patients who progressed too rapidly for drug effects to take place so that local block could be injected. As soon as the procaine took effect delivery was conducted under the local anesthetic alone. This procedure was carried out in 3.5 per cent of deliveries. Such cases can be controlled, if time allows, by intravenous apomorphine repeated at short

intervals. As the technique of altering the routine to suit the individual case was perfected, inhalation was used in only 15.7 per cent of the last 287 cases done.

Perhaps the most satisfactory result of this premedication, particularly striking when no inhalation anesthesia is used, is that all of the babies breathe and cry immediately upon delivery. Of the 525 liveborn babies included in this study only 26, or 4.5 per cent, required resuscitation, and this was shown to be the result of recognized and unavoidable causes involving interference with the infant's circulatory or respiratory mechanism. Such causes included:

1. Cord tight about neck
2. Occult prolapse of cord
3. Separation of placenta in second stage
4. Very rapid labor
5. Long labor with difficult delivery
6. Mucus in air passages
7. Early prematurity

The vital functions of the baby do not seem to be affected by apomorphine. It has been recognized that scopolamine produces no embarrassing effects on the baby and does not lead to hypoxia. Apomorphine has not been shown to produce any observable change in the fetus. There is no depression of the cardiac or respiratory rate. No narcotized babies were delivered; neither has there developed any delayed cyanosis or cardiorespiratory embarrassment during the first twelve hours of extrauterine life.

There were 3 full-term baby deaths in this series. One neonatal death was due to a large patent ductus arteriosus, and two stillborn infants showed intracranial hemorrhage with placental fibrosis and occult prolapse of the cord, respectively. Each case came to autopsy.

The late premature babies ranging betwen 32 and 38 weeks of intrauterine age reacted as well as those born during the last 2 weeks of pregnancy. There were 17 such infants weighing between 4 pounds, 1 ounce, and 5 pounds. Of these there were 2 neonatal deaths and 3 stillbirths. Of the 12 babies surviving, 11 breathed and cried immediately at delivery, and one required resuscitation, being embarrassed by a partial placental separation and an occult prolapse of the cord. In these 12 cases apomorphine dosage ranged from $\frac{1}{100}$ grain to 7 doses of $\frac{1}{50}$ grain. No effect of the premedication was evident in these babies. Definite pathology totally unrelated to the analgesic agents was established in each case of death:

1. Macerated fetus with erythroblastosis
2. Anencephaly and spina bifida
3. Intrauterine asphyxia due to cord tight about neck and prolapsed over shoulder
4. Neonatal death after 2 hours: intrauterine asphyxia due to separation of the placenta
5. Neonatal death after 2 days: fulminating toxemia of mother with retinal hemorrhages

The third stage of labor is unaffected and there is no apparent increase of blood loss. The return to consciousness is rapid, the patient awakening in a happy frame of mind. A quiet emergence from amnesia or anesthesia is assured if $\frac{1}{6}$ grain of morphine or $\frac{1}{100}$ grain of apomorphine is given before the patient leaves the delivery room. Apomorphine is preferable, thus obviating the incidental depression that may follow postpartum morphine in the occasional case.

In most cases the patient recognizes her husband when he makes his first postpartum visit at the bedside and he is able to have the pleasure of informing his wife of the arrival of the new member of the family. Recovery is quick and smooth. Disturbances of gastrointestinal function and of elimination are absent. Patients are usually pleased with their experience. They are hungry, eat excellent meals from the start, and are eager to get out of bed as soon as allowed, usually the day after delivery.

On the second postpartum day the patients are questioned concerning their labor experience. If delayed beyond this their statements become colored by the telling, and influenced by conversation with roommates, relatives, nurses, and others. Most of them report a comfortable labor with at most 2 or 3 hard pains after the first injection, or they report no memory of the whole event.

The patients having a complete amnesia with absence of excitement, or in whom agitation was obviously controlled by apomorphine, were classified as "excellent" (87 per cent) (Table VI). Those who retained vague memory of disconnected incidents, or whose excitement was only partially controlled were tabulated as "fair" (9.5 per cent). The failures were denoted as "poor" (3.5 per cent), having clear memory of many incidents, recalling "a painful labor," and developing excitement unaffected by apomorphine. This group is composed chiefly of women who are high strung, sensitive, or lacking in self-discipline, as well as those who have recently suffered a deep loss, or are extremely apprehensive. These patients are uncontrollable under apomorphine-scopolamine, and agents of a narcotic nature are necessary for their proper management. However, with better timing and more frequent use of apomorphine intravenously it is felt that these results can be improved.

TABLE VI. MATERNAL EFFECTS

		NUMBER	PER CENT
Excellent:	No excitement, no memory, or excitement controlled	460	87.0
Fair:	Excitement partially controlled, islands of memory	50	9.5
Poor:	Excitement not controlled, consecutive memory	20	3.5
Total		530	100.0

Vomiting occurred in 25 per cent of the early cases of this series; but the simple expedient of giving the injection more slowly reduced the emesis rate to 10 per cent in later cases. This is not alarming or objectionable for several reasons:

1. Many patients who have received no medication will vomit when the contractions become hard, or upon approaching the second stage.
2. Some patients will vomit after almost any medication for labor.
3. Any patient who has recently eaten will vomit after apomorphine.
4. If the patient vomits, a quiet slumber soon ensues.
5. At delivery a patient with an empty stomach under apomorphine does not present to the anesthetist the problem of aspiration of vomitus.
6. An empty stomach favors a comfortable and rapid convalescence.

If, as it would seem, an empty stomach is advantageous during labor, the stimulation of emesis should provide an additional factor of safety. The dosage schedules start with $\frac{1}{100}$ grain in order to pick up hypersensitivity. One patient fell into this category as she vomited for about 3 hours following the first dose of $\frac{1}{100}$ grain.

The reaction of patients under this medication is that of scopolamine effect except that restlessness is uncommon. They sleep quietly between pains, stirring or rolling over and mumbling disconnectedly with the harder contractions. Flushed skin, dry mouth, slight increased respiratory rate are scopolamine effects. No change in pulse or blood pressure is noted. No muscle twitchings or convulsive movements occur. Generalized hyperesthesia of the skin is noted in many cases causing the patient to jump or pull away when touched. This seems more definite in the presence of apomorphine than with scopolamine alone, and may be part of the excitant influence exerted on the central nervous system by apomorphine, not altogether due to scopolamine.

No lasting effects have been observed. There were no postpartum respiratory complications. When these drugs were given to women with upper respiratory infections, the process regressed and the patients benefited by the drugs, possibly because of the expectorant effect of apomorphine; no increased moisture in the lungs was noted.

It was noted in several instances that labor seemed to be slowed after the medication was started. If given too early, before progress is actually in evidence by changes in the cervix, this may happen. Real progressive labor, however, appears to be shorter under apomorphine-scopolamine. Tabulations of the length of labor are not included in this paper, since the shortening effect was amply demonstrated in Hershenson's[2] article, averaging 11.3 hours in primiparas and 6.5 hours in multiparas. No case of atony of the uterus could be ascribed to the method. Long labors occasionally required a total dose of $\frac{1}{10}$ to $\frac{1}{5}$ grain of apomorphine but no untoward effect on the mother, infant, or the labor could be noted. There was no cumulative effect, and recovery was just as rapid as when fewer doses were given. There were no maternal deaths. The safety of apomorphine for the mother seems outstanding.

Apomorphine is contraindicated in conditions which would suffer from the mere act of vomiting should it be induced, or in which the consequent depression and muscular weakness would be dangerous to the well-being of the patient. Such conditions include debilitation, actual or impending cardiac decompensation, shock, respiratory obstruction, and pulmonary edema, especially when associated with eclampsia. It would be hazardous to use apomorphine in the presence of certain esophageal lesions such as diverticulum, stricture, or ulcer, because of possible rupture secondary to vomiting. Scopolamine with apomorphine obviously should be avoided in conditions in which production of cortical excitement is unwise as in cardiac embarrassment and in patients who are in an unusually agitated or apprehensive state of mind.

Amnesia-analgesia achieved in this series compares favorably with the best results reported by almost any other method. Also we can confirm the claim for apomorphine that it will with few exceptions control the excitement induced by scopolamine. Success with the combination is enhanced by experience and close attention to the patient, shifting the timing and dosage according to her behavior.

Summary and Conclusions

Apomorphine-scopolamine amnesia-analgesia was used in 704 private cases in labor at the Orange Memorial Hospital. The results of the detailed study of 530 of these cases are reported.

This study was undertaken to investigate the usefulness and safety of this combination. It has proved a valuable and dependable agent to produce both

amnesia and analgesia, its effects comparing favorably with those of other methods. The safety factor is outstanding in that no deleterious effects, immediate or late, could be elicited in mother or infant.

Apomorphine-scopolamine may be administered at any time in labor and by the intramuscular or intravenous route without affecting the normal course of labor. They may be used in conjunction with other methods of analgesia. Cortical excitement, a frequent objectionable side effect of scopolamine, can almost always be controlled by the proper use of apomorphine.

Apomorphine potentiates the analgesia of scopolamine. The analgesia produced is frequently sufficient to allow complete delivery to take place without supplementary anesthesia. The combination seems particularly suited to the employment of regional or local anesthesia for delivery. The need for inhalation anesthesia is diminished.

The natural forces of the mother in the second stage of labor are brought into play more efficiently with this method of pain relief than with any other agents we have observed. The mother's energy is not dissipated but rather converted to useful and effective progress.

The third stage of labor is not affected.

A beneficial effect on upper respiratory infections is noted in patients who have been given this drug.

One case of sensitivity with prolonged vomiting was encountered.

Evidence of interference with the vital processes of the fetus is absent. When delayed respiratory response occurs specific physical cause of hypoxia can be demonstrated.

There were 3 deaths of full-term babies. Postmortem examination revealed no relation to the drugs used in labor.

Apomorphine-scopolamine is not contraindicated in premature labor after the thirty-second week because all babies in the absence of fetal and maternal pathology exhibited immediate respiratory response and did well thereafter.

It is pointed out that success with apomorphine-scopolamine increases with experience and development of skill and timing. More frequent use of the intravenous route for administration of apomorphine will speed and increase the analgesia desired. It will appreciably decrease the need and amount of supplementary anesthesia used for delivery, and will progressively reduce the incidence of operative procedures.

There is a definite need for investigative study of subemetic doses of apomorphine hydrochloride in its pharmacologic-obstetrical relationships, for it is a valuable addition to the obstetrician's equipment.

Addendum

Since the completion of this series, data on the next 100 patients delivered demonstrate improvement in some respects gained by experience with this combination:

1. Control of excitement, the same.
2. Freedom from fetal distress, the same.

3. Anesthesia used:

None	18%	against 10.50%	reported in this paper
Inhalation only	3%	against 32.85%	reported in this paper
Local only	75%	against 53.10%	reported in this paper
Inhalation plus local	4%	against 3.55%	reported in this paper

4. Vomiting 2% against 25% in early cases reported and 10% in later cases reported

5. Apomorphine controlled emergence excitement better than morphine in some cases observed.

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144 South Harrison Street

OXYTOCIC AND TOXIC ACTIONS OF DIHYDROERGOTAMINE-45*

SHELDON G. ALTMAN, M.D.,** RICHARD WALTMAN, M.D., F.A.C.S., AND
SAMUEL LUBIN, M.D., F.A.C.S., BROOKLYN, N. Y., AND
SAMUEL R. M. REYNOLDS, PH.D., D.SC.,
BALTIMORE, MD.

(From the Department of Obstetrics and Gynecology, College of Medicine, State University of New York, Cumberland Hospital, Brooklyn, N. Y., and from the Department of Embryology, Carnegie Institution of Washington)

IN MODERN obstetrics efforts are made to decrease maternal and fetal mortality and morbidity. With antibiotics, blood transfusions, improved prenatal care, and better anesthesia, childbearing is becoming safer. Attempts are made to shorten labor and to inquire into the factors which cause uterine inertia. The use of Pitocin intravenously has proved to be useful for this purpose when in the hands of competent obstetricians.

Recently, in this country and abroad, Dihydroergotamine-45 has been used in obstetrics. Orth and Richie[1] found that Dihydroergotamine-45 was not oxytocic when tested on the rat uterus in vivo or in vitro. When Dihydroergotamine-45 was injected daily into pregnant rats, it was without effect on mother or offspring. In quite large doses, the drug was without toxic action. Sauter,[2] experimenting with sympathicolytic drugs, reported that Dihydroergotamine-45 shortened prolonged labor supposedly due to cervical spasm. Other drugs, including pituitary preparations administered intramuscularly, were ineffective. In 30 of 43 cases of alleged cervical spasm in which 0.25 to 0.50 mg. of Dihydroergotamine-45 was given intramuscularly or intravenously, the cervix is stated to have relaxed without stimulation of the fundus. Reist,[3] treating 50 cases of supposed cervical spasm, claimed to have confirmed these findings. Gill and Farrar[4] reported 80 per cent useful results in a series of 43 cases of uterine inertia and "cervical spasm." They administered 0.25 mg. of Dihydroergotamine -45 intramuscularly, repeating the dose as often as three times at four-hour intervals. They concluded that the drug was useful as a sympathicolytic drug, was oxytocic, and not harmful. It was also their opinion that the drug was of no value unless painful contractions were present. Baskin and Crealock[5, 6] claim to have used Dihydroergotamine-45 successfully. These authors administered the drug intravenously, in a concentration of 1 mg. per cubic centimeter. They concluded that Dihydroergotamine-45 is a safe, nontoxic drug, useful in relaxing a spastic cervix and in shortening labor.

The favorable reports of all of these authors claiming relaxation of the cervix and the hastening of delivery with the use of Dihydroergotamine-45 led us to try this drug clinically at Cumberland Hospital and to evaluate its effect upon the uterus with the aid of a two-channel tokodynamometer.

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**Research Fellow, Department of Obstetrics and Gynecology, Cumberland Hospital, Brooklyn, N. Y.

The basic pharmacological studies of ergot preparations were done by Dale.[7] Advances in knowledge of the pharmacology and of the clinical applications of ergot substances have resulted in a generally accepted classification of the effects of the ergot alkaloids.[8] These are as follows:

1. Effects which have their point of attack in the central nervous system (e.g., as manifested by respiration, pulse rate, blood pressure, temperature, emesis, and sedation).
2. Effects with peripheral points of attack:
   a. Visible actions (e.g., stimulation of smooth muscle organs, especially the uterus and blood vessels).
   b. Latent sympathicolytic actions, such as the interruption of response, if it is mediated by stimulation of a sympathetic nerve or Adrenalin.

Ergotamine is the least toxic of the ergot alkaloids.[8] The ergotamine molecule contains lysergic acid, a characteristic moiety of all the natural ergot alkaloids. This is a nonsaturated aromatic acid containing five double bonds (C=C), one of which can be saturated individually.[9] The hydrogenation of ergotamine at this point results in the formation of a well-defined, stable compound, Dihydroergotamine-45, which is one-eighth as toxic as the original ergotamine.[8]

For the purpose of this present study, four properties of ergotamine need be considered. They are the oxytocic, sympathicolytic, vasopressive and emetic effects. The hydrogenation process supposedly removed all except the sympathicolytic effect. The sympathicolytic property has been the basis of the use of Dihydroergotamine-45 in "cervical spasm" and uterine inertia.

According to Reist[3] cervical spasm is only a local symptom of a hypertonic condition existing in the entire uterus. Thus, Dihydroergotamine-45 should reduce the "tone" of the uterus and enable the uterus to contract with greater intensity, as observed by the amplitude of the uterine contraction on the tokodynamometer.

With these facts in mind, the following study was undertaken.

Method

One mg. of Dihydroergotamine methanesulfonate (Dihydroergotamine-45) was added to 500 c.c. of distilled water. This solution was administered intravenously at the rate of 3 to 3½ c.c. per minute to pregnant patients selected for study. The rate of flow was adjusted if the fetal heart rate became slow or irregular. The patients received 500 c.c. of solution over a period of two to four hours. By intravenous administration of the drug, its effects could be observed better, the rate of administration controlled, and its use terminated quickly if necessary.

Material

Eight primigravidas and twelve multigravidas were available for study. A two-channel strain gauge tokodynamometer was placed on the patient's abdomen, one lead in the midline over the contractile portion of the fundus and one lead in the midline several inches above the symphysis pubis. The latter strain gauge was considered to be in the vicinity of the lower uterine segment.[10] A 30 minute recording was taken before the drug was started. The fetal heart rate was under constant observation, as was the systemic blood pressure as well. No sedation was given prior to the administration of the Dihydroergotamine-45, but, during the infusion, 100 mg. of Demerol (2 c.c.) were given intravenously when the patient complained of disturbing pain. No other drugs were used.

The oxytocic effects of the drug were judged by the frequency and amplitude of the uterine contractions as recorded by the tokodynamometer. A sympathicolytic effect on the lower part of the uterus, if any, could be shown by the tokodynamometer as a change in base line. A lowering of blood pressure likewise would indicate a sympathicolytic action of the drug. The blood pressure was considered to have been affected if there was a 10 mm. of mercury decrease in either the systolic or diastolic pressure, sustained for a 10 minute period. In addition, the sympathicolytic effect was estimated clinically by the softening of the cervix judged by rectal and vaginal examinations.

Of the eight primigravidas, one was not in labor. She had intact membranes. Three primigravidas had intact membranes and their cervices were less than 4 cm. dilated. Seven patients had intact membranes. The other had ruptured membranes. None of the twelve multigravidas was in labor. Four had ruptured membranes. The ages of the patients ranged from 17 to 32 years.

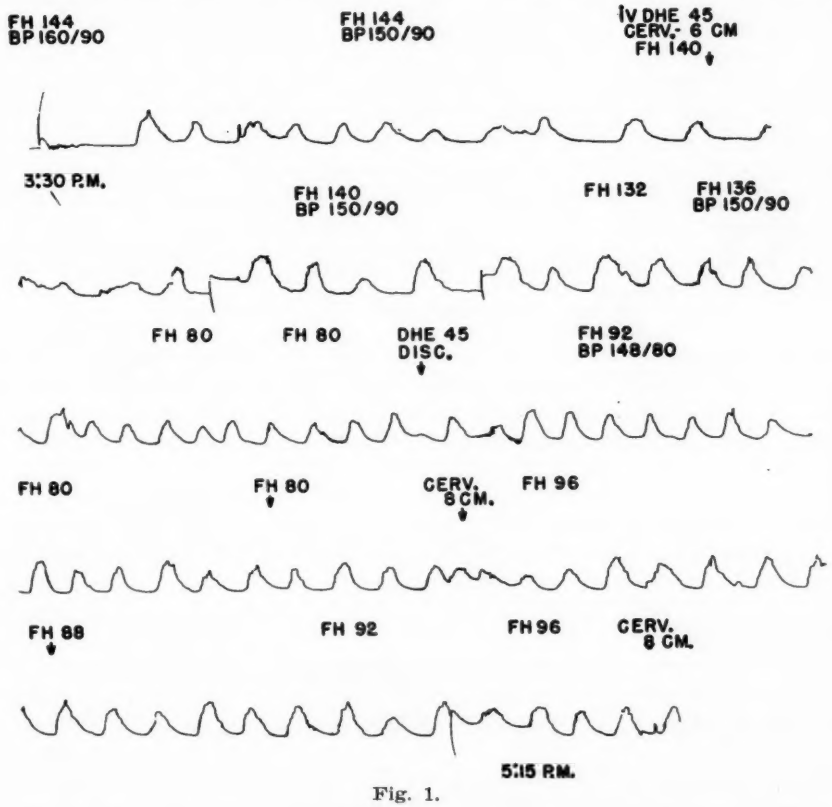

Fig. 1.

Contrary to the findings of Rothlin,[8] who stated that Dihydroergotamine-45 is not oxytocic in tests on animals' uteri, we found in all twenty women that uterine contractions were improved, as evidenced by increase in amplitude and frequency of contractions. In addition, where no contractions were present at the outset, they were initiated. (This occurred in one primigravid and in 12 multigravid patients.) It is important to note that when Dihydroergotamine-45 was given to women not in labor, and when labor was not induced, the contractions which were initiated during the administration ceased promptly upon withdrawal of Dihydroergotamine-45 (Figs. 1, 2, and 3).

In fourteen women, there were definite indications of the sympathicolytic effect of Dihydroergotamine-45. This was demonstrated by either a decrease

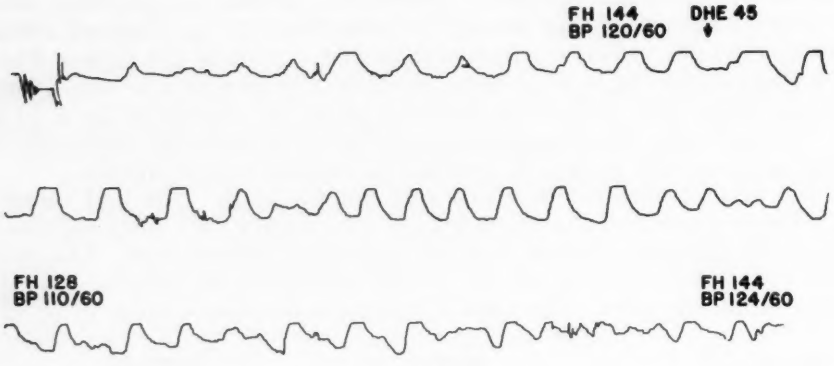
FH 144
BP 120/60
DHE 45
FH 128
BP 110/60
FH 144
BP 124/60

Fig. 2.

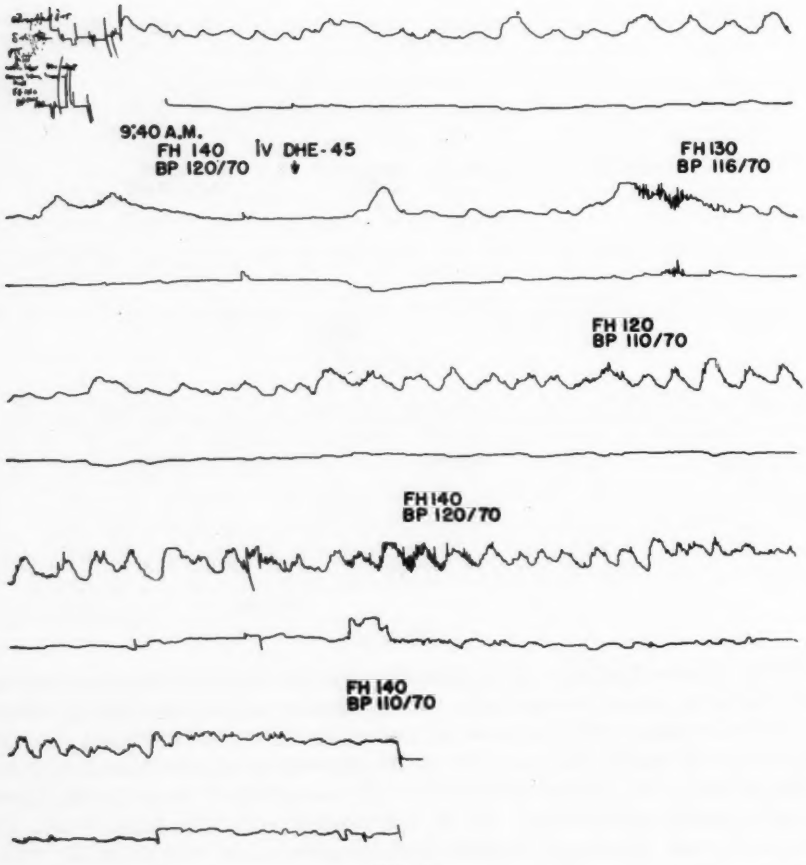
9:40 A.M.
FH 140
BP 120/70
IV DHE-45
FH 130
BP 116/70
FH 120
BP 110/70
FH 140
BP 120/70
FH 140
BP 110/70

Fig. 3.

in the level of the base line of the record obtained over the lower portion of the uterus, a decrease in the systemic blood pressure, or a softening of the cervix (Fig. 3).

The blood pressure was decreased in 55 per cent of the cases. The maximum drop was 20 mm. of mercury in both systolic and diastolic pressures observed in two cases. In two cases, a transient increase in systolic pressure of 20 mm. was noted.

There were two unfavorable maternal effects of the drug. Three patients had intermittent nausea. This was also the experience of Baskin and Crealock.[5] In our series, however, the patients who had nausea vomited. In addition, three patients developed a transient hematuria. One woman exhibited hematuria after 400 c.c. of an intravenous 1:500 infusion of Dihydroergotamine-45. In two cases, hematuria occurred about 12 hours after the drug was administered. Intravenous pyelogram and retrograde cystoscopy revealed no evident abnormalities.

Contrary to the work of Baskin and Crealock,[5] and Gill and Farrar,[4] there were, in our series, eleven (55 per cent) instances of fetal distress. A slowing of the fetal heart rate below a rate of 100 beats per minute sometimes accompanied by an irregularity in the rate was found even though the uterus was not contracting. Such signs are considered to be an indication of fetal distress.[11] In five cases, the fetal embarrassment was transient and the children were born alive and well. However, four women had stillborn babies; one baby died one hour after delivery (see Case 2). A sixth patient had a subdural hematoma without further complication (see Case 4).

Results

The maternal response was varied. The primigravid woman who was not in labor had intact membranes. Her cervix was not dilated and the vertex was presenting at station zero in the left occipitoanterior position. She delivered one hour and 40 minutes after the infusion of Dihydroergotamine-45 was commenced. Three primigravid women in early labor (cervix dilated less than 4 cm.) averaged 11 hours and 50 minutes in labor before the administration of the Dihydroergotamine-45. The average length of time after the administration of the drug until delivery in these cases was two hours. There were four primigravidas who were 4 to 6 cm. dilated (one with ruptured membranes) when infusion was begun. The average time in labor before the Dihydroergotamine-45 was given was 11 hours and 30 minutes. The average duration of labor before Dihydroergotamine-45 was given for all of the primigravid women was 11 hours and 30 minutes, and the duration until delivery after beginning Dihydroergotamine-45 for these eight cases was one hour and 45 minutes.

Since the multigravidas were not in labor, the administration of Dihydroergotamine-45 was an attempt at induction. Four had soft cervices and ruptured membranes. Three had successful induction of labor and delivered uneventfully. The average duration of labor was two hours and 50 minutes. Of the eight multigravidas remaining who had intact membranes, labor was successfully induced in four. The average length of labor in these latter cases was six hours. The average length of labor for all multigravidas with successful induction was four hours and 52 minutes.

In seven of the multigravidas (58 per cent) and in one primigravid patient, labor was induced with Dihydroergotamine-45, the total induction rate being 40 per cent of the entire series. The other attempts at induction resulted in softening of the cervix in two cases and no change in the cervix in three cases. All of these last five patients delivered within 48 hours, two of them delivering macerated stillborn infants. The reports of these cases follow.

Case Reports

CASE 1.—A 24-year-old para iv, gravida vi, abortions ii (one set of twins), was admitted to the hospital for the third time on July 24, 1951. Her expected date of delivery was July 27, 1951. Two previous admissions were for hypertension (140/100), associated with four plus pitting edema of the ankles and four plus proteinuria. The patient signed her release on both occasions after having been put on a toxemia regime. The past history revealed that the patient had had toxemia and stillbirths in the last two pregnancies. She was under close supervision in the Outpatient Department and was readmitted from there because of the severity of the hypertension, edema, and proteinuria. She was again placed on a toxemia regime and her blood pressure during the next two weeks ranged from 140/100 to 130/70. The urine continued to show a three plus proteinuria. The blood chemistry and renal function tests were normal.

In an attempt to induce labor on Aug. 7, 1951, for poor patient control of toxemia, an intravenous infusion of Dihydroergotamine-45, 1:500, was started. The membranes were intact, the cervix 2 cm. dilated, the vertex at a minus two station, and the fetal heart rate was 140 per minute. After the infusion, there was no change in the cervical effacement, amount of dilatation, the blood pressure, or the fetal heart rate. Twelve hours later, the patient had a transient hematuria. Twenty-eight hours later she began to labor spontaneously, at which time the fetal heartbeat was not heard. Forty-two hours after the administration of Dihydroergotamine-45, a 4 pound, 8 ounce macerated stillborn fetus was delivered spontaneously. Autopsy revealed only pulmonary atelectasis and visceral congestion.

CASE 2.—A 24-year-old para ii, gravida iv, abortions i, was admitted to the hospital on Aug. 14, 1951, in false labor and discharged the next day. Her expected date of delivery was Sept. 12, 1951. On Oct. 4, 1951, the patient was readmitted. The physical examination was negative with the presence of a full-term pregnancy. The cervix was soft, thick, and not dilated, and the presenting vertex was at minus one station. The blood pressure was 94/62 and the fetal heart rate, 114 beats per minute, was regular in the right lower quadrant. An intravenous infusion of Dihydroergotamine-45, 1:500 dilution, was begun and 100 mg. of Demerol were given one hour later because of pain. Upon completion of the infusion one and one-half hours later, the fetal heart rate was regular at 168 beats per minute in the right lower quadrant. Three hours afterward the membranes ruptured spontaneously, and, within 45 minutes, the patient had a normal spontaneous delivery. The child did not breathe spontaneously but responded to aspiration, oxygen administration, and stimulation. One-half hour after delivery, blood-stained fluid was seen draining from the child's nose. This fluid was identified as bloody spinal fluid. The child became cyanotic and died one hour and 15 minutes after delivery. The autopsy findings were subdural hemorrhage, visceral and cerebral hemorrhages, and pulmonary edema.

CASE 3.—A 25-year-old para i, gravida ii, was admitted in false labor on Aug. 11, 1951. Her expected date of delivery was July 17, 1951. Her antepartum course in the Outpatient Department was normal. The patient had congenital syphilis which was treated when she was six months old. The physical examination, including the presence of a full-term pregnancy in the left occipitoanterior position, was normal. The blood pressure was 128/78; the fetal heart rate was regular at 144 beats per minute in the left lower quadrant. The cervix was uneffaced, not dilated, and the vertex not engaged. Two days later, on Aug. 14, 1951, there was no change in the cervix and the vertex was at a minus two station, and the membranes intact. An intravenous infusion of Dihydroergotamine-45, 1:500 dilution, was administered. The fetal heart was heard during and at the completion of the infusion, which caused no change or effacement in the cervical dilatation. Twenty-four hours later, the fetal heart was not heard, and 24 hours still later, on Aug. 16, 1951, a macerated stillborn fetus was delivered spontaneously. The autopsy showed pulmonary atelectasis and visceral autolysis.

CASE 4.—A 24-year-old para 0, gravida i, was admitted at term on Oct. 8, 1951, in labor. Her expected date of delivery was Oct. 7, 1951. The antepartum course was normal and she was managed in the Outpatient Department. The past history was noncontributory and the physical examination revealed the presence of a full-term gestation in the left occipitoanterior position. The blood pressure was 112/62. The cervix was dilated 6 cm., the membranes were intact, and the vertex was at plus one station. The fetal heart rate was 140 beats per minute, regular, and in the left lower quadrant. An intravenous infusion of Dihydroergotamine-45, 1:500 dilution, was begun followed by Demerol, 100 mg. given intravenously, one hour later. After 10 minutes, the fetal heart rate decreased to 80 beats per minute and it was irregular; after a 10 minute interval of time during which the fetal heart remained at 80 and irregular, the Dihydroergotamine-45 infusion was discontinued. The fetal heart rate remained irregular and below 100. The membranes were then ruptured artificially and the fetal heart rate returned to normal (120 beats per minute) in one-half hour. Forty minutes later, the patient was delivered with outlet forceps and an episiotomy from an anterior position. The child was sluggish at birth, breathed poorly, and did not cry spontaneously. He was aspirated and given oxygen. Three days later the child developed convulsions. A spinal tap showed bloody fluid and a diagnosis of subdural hematoma was made. The child, at the time of the present writing, is 3 months old and is progressing satisfactorily with no abnormal neurological signs.

CASE 5.—A 21-year-old para 0, gravida i, was admitted in labor on Sept. 19, 1951, at term. Her expected date of delivery was Sept. 12, 1951. She had an uneventful antenatal course and was managed in the Outpatient Department. The past history was noncontributory and the physical examination was essentially normal with the presence of a full-term gestation in the left occipitoanterior position. The cervix was 2 cm. dilated and the vertex was at station zero. The membranes were intact, and the fetal heart rate was regular, 140, and in the left lower quadrant. An intravenous infusion of Dihydroergotamine-45, 1:500 dilution, was begun, followed by 100 mg. of Demerol intravenously one hour later. Three hours later the cervix was fully dilated and the fetal heart rate was 148 beats per minute, regular. Forty-five minutes later, the patient had a normal spontaneous delivery of a stillborn child. There were two loops of umbilical cord around the neck. An autopsy was not made. This case is similar to Case 3 of Gill and Farrar[4] where Dihydroergotamine-45 was given three hours before delivery. The fetal heart rate became irregular 20 minutes before delivery. Autopsy suggested intrauterine asphyxia.

CASE 6.—A 30-year-old, para ii, gravida iii, was admitted on Oct. 2, 1951, because of ruptured membranes of 24 hours' duration. The expected date of delivery was Oct. 14, 1951. The patient was not in labor. She had a normal antenatal course and had been followed in the Outpatient Department. The past history was noncontributory and the physical examination was essentially normal with the presence of a full-term gestation in the right occipitoanterior position.

On Oct. 3, 1951, the cervix was thick, uneffaced, and not dilated. The vertex was unengaged, the fetal heart rate was 132 and regular. It was heard in the lower right quadrant. The blood pressure was 110/80. An intravenous infusion of Dihydroergotamine-45, 1:500 dilution, was begun. Two hours later, 100 mg. of Demerol were slowly injected intravenously. Fifteen minutes later, the fetal heart rate was irregular and slow, 68, and 20 minutes later a stillborn child was delivered spontaneously. There was one loop of umbilical cord around the neck. The umbilical cord was longer than average, and had a tight true knot in it. The autopsy findings were those of pulmonary atelectasis and visceral hemorrhages.

Comment

From the results reported above, it is clear that Dihydroergotamine-45 has a striking effect on the entire uterus. It has been said and accepted that Dihydroergotamine-45 is a sympathicolytic drug. Our experience is not in-

compatible with this view but it does not depend upon such an interpretation either. We have found, in addition, that there is frequently a very strong oxytocic action. Dihydroergotamine-45 has relaxed the cervix in several instances, as well as the upper uterine segment. This relaxation could account in part for the increased amplitude of the uterine contractions. However, Dihydroergotamine-45 also has a marked and characteristic effect on contractility, increasing the frequency. The fact that Dihydroergotamine-45 may relax the lower portion of the uterus could make it a valuable drug. Its oxytocic action would then enhance its influence in the obstetrical armamentarium. Because of the high incidence of fetal loss (25 per cent), and the signs of fetal distress in another 30 per cent, it is believed that the risk is too great and the use of this drug in labor constitutes a dangerous practice. It is entirely possible that not all of the fetal accidents were due to the Dihydroergotamine-45. In one case there was a tight true knot in the umbilical cord and in another case, there was associated a severe toxemia. Discounting these two cases, it leaves a corrected fetal loss of 15 per cent. This percentage is still too high to justify its use, leaving the burden of proof on those still desiring to employ the drug as an aid to cervical dilatation.

There is yet another reason for extreme caution in the use of Dihydroergotamine-45. This is that a side effect, not previously reported, was encountered. Hematuria occurred in three of the cases (15 per cent). Since the examination of the genitourinary systems exposed no etiological factors for this sign, we must logically conclude that the Dihydroergotamine-45 was responsible for this complication, too.

It is believed that there may be a relationship between Demerol and Dihydroergotamine-45, because when the Demerol was given to two of the patients receiving the Dihydroergotamine-45, the signs of fetal embarrassment began within 15 minutes. The mechanism of this, if true, is not known.

Monckeberg[12] gave Dihydroergotamine-45 to a series of 100 women in labor. The drug, 0.25 mg. intravenously, was repeated three or four times at three-hour intervals as necessary. He concluded that the effect depended upon the dosage, single doses improving contractions already present and relaxing the cervix. He recommended repeated doses for induction. When administered to patients whose cervices were dilated 5 to 6 cm., the average time till delivery was 25 minutes. This confirms the work of Baskin and Crealock.[6]

In cases of prolonged labor, satisfactory results were obtained in 70 per cent of the cases. Thirty per cent of the cases of cervical dystocia did not react. There were three cases of fetal death in the series reported by Monckeberg; two, it is reported, not related to the use of the drug as shown by autopsy. The other case was similar to one of our series (Case 1), in which there was toxemia and induction was attempted with Dihydroergotamine-45. A macerated stillborn child was delivered about a day and a half later. It was believed that the fetal heart and blood pressure changes, which were similar to those reported in this paper, were not significant. Monckeberg does state that Dihydroergotamine-45 should not be used for induction of labor because of the large doses necessary which probably are harmful.

We agree that Dihydroergotamine-45 does improve uterine contractions and it may induce labor. We also feel that this drug causes changes in the fetal heart which are significant and unfavorable.

That the entire range of effects of Dihydroergotamine-45 is not known is readily admitted. Alvarez[13] reports a case of a pregnant woman suffering with migraine headaches who received almost daily injections of Dihydroergotamine-45 for the greater part of her pregnancy and delivered a normal child.

Conclusions

1. Dihydroergotamine-45 is an agent for producing relaxation of the uterine "tone," possibly including that of the cervix.

2. Dihydroergotamine-45 is oxytocic. It increases the strength and frequency of contractions.

3. Dihydroergotamine-45 as used in this manner (1 mg. in 500 c.c. of water given by intravenous infusion) can induce labor.

4. The average length of labor is shortened in both primigravidas and multigravidas with the use of intravenous Dihydroergotamine-45.

5. Intravenous Dihydroergotamine-45, 1:500 dilution, gives rise to undesirable side effects such as a high proportion of fetal loss and hematuria.

6. The toxic effects associated with the use of Dihydroergotamine-45 should caution us against its use as an aid to labor.

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847 Park Place

FETAL AND NEONATAL RESULTS IN BREECH PRESENTATION IN THE PRIMIPAROUS PATIENT AT TERM

WILLIAM POMERANCE, M.D., F.A.C.S., AND ISIDORE DAICHMAN, M.D., F.A.C.S.,
BROOKLYN, N. Y.

(From the Jewish Hospital of Brooklyn)

WHILE the fetal mortality for breech delivery has been variously given as ranging from 3.8 to 52 per cent, it is quite clear that the corrected fetal mortality for term fetuses is somewhat less than 5 per cent (Dieckmann, Cox). What part of this fetal loss is directly attributable to the abnormal presentation is, as yet, not as clear. Also what readily discernible clinical characteristics are associated with the high fetal losses are likewise not clear. This report is an attempt to reach some conclusion in regard to these last two considerations.

Material

This study is concerned with 716 breech presentations occurring in primiparous patients during the years 1939 through 1948 at the Jewish Hospital of Brooklyn. All of these cases were primary breech presentations and in each case only a single fetus was present, and in each case the fetus weighed 5 pounds or over. Multiparas were not studied because it was felt that a separate review of these should be made. Multiple births also were omitted because these included other complications besides the one of presentation. Likewise, fetuses under 5 pounds were excluded because they represented an additional complicating factor of prematurity that seemed to be beyond the scope of this paper.

These 716 cases included 621 (86.7 per cent) patients delivered vaginally and 95 (13.3 per cent) patients delivered by cesarean section. The former group was analyzed as to the influence of age of the patient, weight of the fetus, method of delivery, duration of labor, duration of second stage, type of breech presentation, and duration of ruptured membranes.

Incidence.—There were 41,135 deliveries at the Jewish Hospital during the years studied. Of these, 19,498 were primiparous patients; and of these 18,387 infants weighed 5 pounds or over. Therefore, our incidence of breech presentation in primiparous patients with fetuses weighing 5 pounds or over was 3.9 per cent (Table I).

Fetal and Neonatal Loss.—There were 32 stillbirths and neonatal deaths, or an uncorrected fetal loss of 4.5 per cent. However, since all of our fetal and neonatal loss occurred in vaginal deliveries, we have related this figure to the 621 vaginal deliveries, or a loss of 5.1 per cent. This figure should be compared with our figure of 1.4 per cent fetal and neonatal loss occurring at our hospital in all fetuses 5 pounds or over, indicating an approximate loss of 3.7 per cent due to the vaginal delivery of such fetuses in primiparous patients. An approximation is likewise obtained by correcting the fetal and neonatal loss for antepartum deaths (3 cases) and for fetal abnormality inconsistent

with life (2 cases) and for neonatal infection (1 case), which resulted in a fetal loss figure of 4.2 per cent (Table II). It seems, therefore, that it can be safely said that vaginal delivery of a fetus weighing over 5 pounds increases the fetal loss approximately 4 per cent.

TABLE I. BREECH PRESENTATION IN PRIMIPAROUS DELIVERIES

Total number of deliveries	41,135
Total number of primiparous deliveries	19,498
Total number of primiparous deliveries, infants 5 pounds or over	18,387
Total number of primiparous breech deliveries	716 (3.9%)

The 26 fetal and neonatal deaths occurring in the 615 vaginal deliveries are analyzed with respect to certain clinical variations as noted above. These are presented in table and chart form and are herewith summarized.

TABLE II. CORRECTED FETAL AND NEONATAL LOSS FOR VAGINAL DELIVERIES

		NUMBER OF CASES	PERCENTAGE OF CASES
Number of cases	621	32	5.1
Corrected for antepartum fetal deaths	618	29	4.7
Corrected for fetal abnormality and neonatal infection	615	26	4.2

Fetal results in relation to the weight of the fetus: An analysis of Table III and Fig. 1 shows that when the fetus weighs 9 pounds or over there is a marked increase in the fetal and neonatal loss and only a moderate variation below that weight level.

Fetal results in relation to age of patient: Table IV shows that there is no relationship between the age of the patient and fetal and neonatal loss.

TABLE III. FETAL AND NEONATAL LOSS IN RELATION TO WEIGHT OF FETUS

WEIGHT OF FETUS	NUMBER	FETAL AND NEONATAL LOSS	
		NUMBER	PERCENTAGE
5 pounds to 5 pounds, 15 ounces	88	4	4.5
6 pounds to 6 pounds, 15 ounces	232	5	2.1
7 pounds to 7 pounds, 15 ounces	207	10	4.8
8 pounds to 8 pounds, 15 ounces	68	2	2.9
9 pounds and over	20	5	25.0
Total	615	26	4.2

Fetal results in relation to method of delivery: When breech extraction is necessary the fetal loss increases moderately (from 1.7 per cent to 4.0 per cent) and when breech extraction and forceps on the after-coming head (which are not used routinely at our hospital) are necessary, the fetal and neonatal losses are increased very considerably (from 4.0 per cent to 14.5 per cent).

TABLE IV. FETAL AND NEONATAL LOSS IN RELATION TO AGE OF PATIENT

AGE OF PATIENT IN YEARS	NUMBER OF PATIENTS	FETAL AND NEONATAL LOSS	
		NUMBER	PERCENTAGE
Under 20	20	1	5.0
20 to 29	450	18	4.0
30 to 39	140	7	5.0
40 and over	5	0	0.0
Total	615	26	4.2

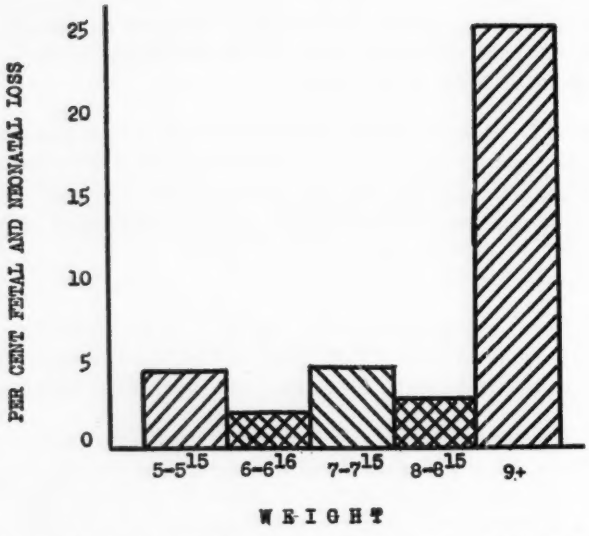

Fig. 1.—Fetal and neonatal loss in relation to weight of fetus.

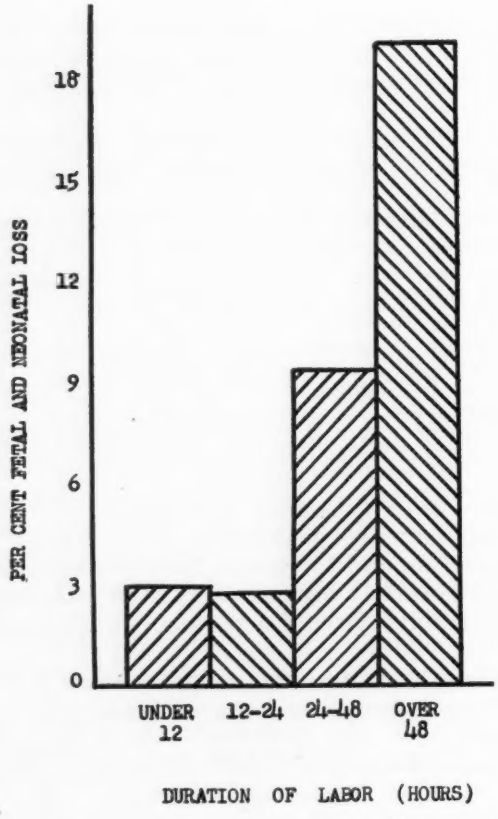

Fig. 2.—Fetal and neonatal loss in relation to duration of labor.

Fetal result in relation to total duration of labor: Table V and Fig. 2 show that the fetal and neonatal loss increases considerably when the labor is over 24 hours and quite markedly when the labor is over 48 hours.

TABLE V. FETAL AND NEONATAL LOSS IN RELATION TO DURATION OF LABOR

DURATION OF LABOR (HOURS)	NUMBER OF PATIENTS	FETAL AND NEONATAL LOSS	
		NUMBER	PERCENTAGE
Under 12	304	9	2.9
12 to 24	215	6	2.7
24 to 48	75	7	9.3
Over 48	21	4	19.0
Total	615	26	4.2

Fetal result in relation to duration of second stage: Table VI and Fig. 3 show a slight increase in fetal and neonatal loss when the second stage is under a half-hour and a considerable increase in such loss when the second stage is over two hours.

TABLE VI. FETAL AND NEONATAL LOSS IN RELATION TO DURATION OF SECOND STAGE

DURATION OF SECOND STAGE (HOURS)	NUMBER OF PATIENTS	FETAL AND NEONATAL LOSS	
		NUMBER	PERCENTAGE
Under one-half	137	7	5.1
One-half to one	186	6	3.2
One to two	200	6	3.0
Over two	85	7	8.2
Unknown	7	0	0.0
Total	615	26	4.2

Fetal result in relation to duration of ruptured membranes: Table VII and Fig. 4 indicate a considerable increase in fetal loss when the membranes are ruptured over 48 hours.

TABLE VII. FETAL AND NEONATAL LOSS IN RELATION TO DURATION OF RUPTURED MEMBRANES

DURATION OF RUPTURED MEMBRANES (HOURS)	NUMBER OF PATIENTS	FETAL AND NEONATAL LOSS	
		NUMBER	PERCENTAGE
Under 12	388	12	3.1
12 to 24	100	3	3.0
24 to 48	64	2	3.1
48 and over	31	5	16.1
Unknown	32	4	12.5
Total	615	26	4.2

Fetal result in relation to type of breech: Analysis of Table VIII shows that complete or footling breech results in a definitely increased fetal loss over frank breech.

TABLE VIII. FETAL AND NEONATAL LOSS IN RELATION TO TYPE OF BREECH

TYPE OF BREECH	NUMBER OF PATIENTS	FETAL AND NEONATAL LOSS	
		NUMBER	PERCENTAGE
Complete and footling	181	11	6.1
Frank	380	14	3.6
Undetermined	54	1	1.9
Total	615	26	4.2

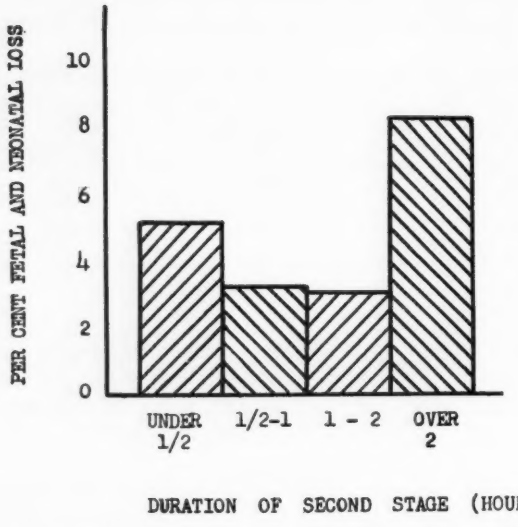

Fig. 3.—Fetal and neonatal loss in relation to duration of second stage.

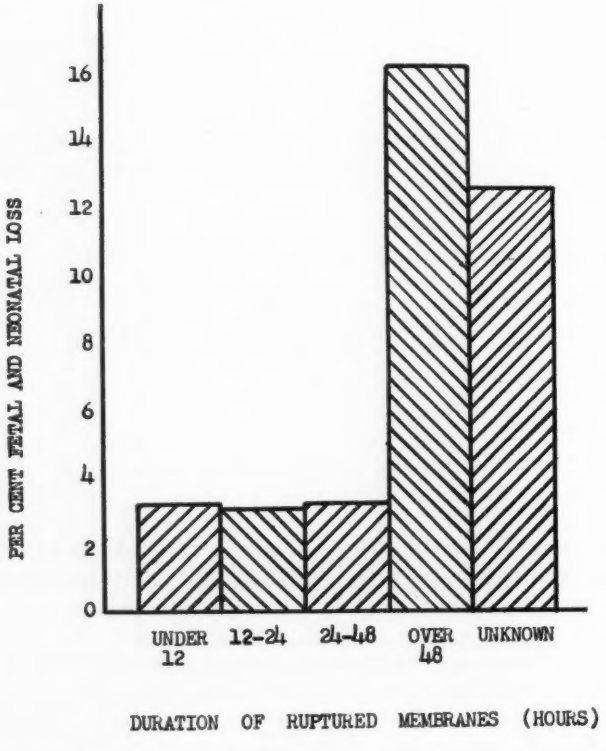

Fig. 4.—Fetal and neonatal loss in relation to duration of ruptured membranes.

Fetal Morbidity.—The fetal morbidity associated with breech presentation is probably as important as the fetal mortality, in so far as many of the injuries (3.7 per cent) are of a permanent and serious nature. In our series there were 11 cases of Erb's palsy, 4 cerebral injuries, 6 fractured long bones, 2 spinal injuries, 1 skull fracture. There were also 5 cases of torticollis and hematoma of sternocleidomastoid muscle and 12 fetal abnormalities (5 had clubfeet, others were cardiacs, spina bifida) (Table IX).

TABLE IX. NEONATAL MORBIDITY IN SURVIVING BABIES

VAGINAL DELIVERY		SECTION	
Erb's palsy	11		
Cerebral injuries	3	Cerebral injury	1
Fracture of long bones	6		
Spinal injuries	2		
Skull fracture	1		
Torticollis and hematomas of sternocleidomastoid	5		
Fetal abnormalities (clubfoot, 5)	12	Fetal abnormalities (clubfoot, 1)	3

Prolapsed Cord.—There were 12 prolapsed cords in our entire series. Nine of the 12 cases were associated with footling presentation. There were 3 stillbirths (25 per cent fetal mortality) among these 12—one ante partum and two intra partum. Nine of the 12 infants were delivered vaginally; all of the stillborn infants were delivered vaginally.

Stillbirths and Neonatal Deaths.—As noted above, of the total of 32 fetal and neonatal deaths, 3 were antepartum deaths. Of the others, 5 fetal deaths occurred during labor, 14 infants were lost during the delivery, and 10 deaths were neonatal (Table X). All 3 antepartum deaths were of infants in footling presentation and one had a prolapsed cord—no other causes for these deaths were ascertainable. Of the 10 neonatal deaths, 7 were due to cerebral injuries, one infant was an anencephalic monster, one died of infection, and one died following surgery for correction of an omphalocele.

TABLE X. STILLBIRTHS AND NEONATAL DEATHS

TOTAL	ANTEPARTUM	INTRAPARTUM, FIRST STAGE	INTRAPARTUM, SECOND STAGE	NEONATAL DEATHS
32	3	5	14	10 Causes: 7 cerebral injury 1 anencephaly 1 infection 1 omphalocele with repair

Cesarean Section.—Of the 716 cases studied, 95, or 13.3 per cent, were delivered by cesarean section (Table XI). Two mothers died (2.1 per cent); the fetal mortality was zero. A brief abstract of the two maternal deaths will be

TABLE XI. FETAL AND NEONATAL LOSS IN PRIMIPAROUS BREECH DELIVERY (INFANTS 5 POUNDS AND OVER)

	NUMBER OF CASES	PERCENTAGE OF TOTAL	FETAL AND NEONATAL LOSS	
			NUMBER	PERCENTAGE
Vaginal deliveries	621	86.7	32	5.1
Cesarean sections	95	13.3	0	0.0
Total	716	100.0	32	4.5

given later. The indications for cesarean section were usually several in number. Elderly primiparity (35 years or over) was an important factor in 27 cases (28.4 per cent). Additional indications were toxemia (6 cases), contracted pelvis (41 cases), sterility (13 cases), uterine inertia (7 cases), large baby, fibroids, double vagina, and prolapsed cord (3 cases). The breech presentation plus some of the above-mentioned indications were the common reasons for doing the section.

Cesarean section has been advocated by some observers in breech presentation when the baby weighs 9 pounds or over (Potter). The reason given for this is the high fetal mortality associated with these very large babies. This particular fact is well brought out in our group of 621 vaginal deliveries. In this group there were 20 babies that weighed 9 or more pounds, and of these, 5, or 25 per cent, were stillborn. In our section group of 95 cases, the large size of the baby, when suspected, was occasionally an additional factor in the decision to do a section, but it was rarely the only factor. Almost every patient with a large breech that was delivered by section had one or more additional indications present which influenced the decision in favor of abdominal delivery.

A study of the duration of labor, duration of ruptured membranes, and type of breech presentation did not yield any particularly worth-while information.

Maternal Mortality.—Two mothers died.

CASE 1.—A 34-year-old primipara, 38 weeks pregnant, with footling presentation and android pelvis, had ruptured membranes for six hours, but no labor. Low flap section and subserous myomectomy were done under general anesthesia. The baby weighed 7 pounds, 2 ounces, and is alive and well. The mother had a temperature elevation for five days. She died suddenly on the sixteenth day. No autopsy was obtained.

CASE 2.—The patient was a 26-year-old primipara at term with ruptured membranes for eight hours, in mild labor with a footling breech and prolapsed cord and a small gynecoid pelvis. Cesarean section was done under local and Pentothal Sodium anesthesia with delivery of a markedly asphyxiated infant that survived with definite cerebral injury. The mother went into shock six hours after operation and died within one hour. There was no autopsy.

Fetal Mortality.—There was no fetal mortality.

Fetal Morbidity.—Of the 95 section babies there was one case of cerebral injury, three fetal deformities, and one clubfoot.

Discussion of Use of Section.—From the above review of our 95 sections, three facts stand out prominently: The fetal mortality of zero, the decreased fetal morbidity, and two maternal deaths. While the absence of any fetal mortality is a worth-while achievement, the loss of two mothers is certainly serious enough to make us realize that there is a definitely increased risk to the mothers. Our average maternal mortality in cesarean section is less than 0.5 per cent; even this figure represents a considerable increase over the maternal mortality by vaginal delivery. We do not believe that one balances the other by any means, and would therefore suggest that the decision to deliver a given case of breech presentation by the abdominal route should be given very serious consideration.

The fetal morbidity is definitely lower by section than by vaginal delivery as is to be expected. This, like the fetal mortality of zero, is very desirable, but, to emphasize again, it is bought at a price of increased maternal mortality.

Summary

1. Seven hundred sixteen cases of single, full-term, primiparous breech presentations were reviewed.

2. An attempt was made to determine the percentage of fetal mortality due to the presentation per se—in this report approximately 3.7 per cent.

3. Cesarean section resulted in an increased fetal salvage, but at an increased maternal cost.

4. Vaginal delivery of babies weighing over 9 pounds resulted in very high fetal loss.

5. Breech extraction with forceps for after-coming head resulted in an increased fetal mortality.

6. Vaginal delivery after 48 hours of labor and/or ruptured membranes for the same period of time resulted in considerably increased fetal loss.

7. Fetal morbidity in the vaginal deliveries was considerable, and in many instances of a serious nature.

8. Prolapsed cord, usually associated with footling presentation, is also associated with a high fetal loss.

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9 PROSPECT PARK, WEST

SUDDEN MATERNAL DEATH ASSOCIATED WITH AMNIOTIC FLUID EMBOLISM

HAROLD M. SLUDER, B.S., M.D., CHARLOTTE, N. C., AND
FRANK R. LOCK, A.B., M.D., WINSTON-SALEM, N. C.

(From the Department of Obstetrics and Gynecology, the Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital, Winston-Salem)

THE finding of amniotic fluid contents in the pulmonary vessels of eight patients who died suddenly during labor was reported by Steiner and Lushbaugh[1] in 1941. This finding was absent in control cases where intrapartum death resulted from other known causes. Intravenous injections of meconium and unfiltered amniotic fluid into rabbits and dogs produced a similar clinical and pathological picture. The entity could not be reproduced by injecting filtered amniotic fluid.

Since this report was published, amniotic fluid embolism has been demonstrated in a sufficient number of cases[1-18] to establish this condition as a cause of sudden death during labor or in the early puerperium. The true incidence of the entity is difficult to determine. Steiner and Lushbaugh[1] originally estimated it to be one in 8,000 confinements, this figure being based on the occurrence of three cases in the first 24,000 deliveries at the new Chicago Lying-in Hospital; however, no further cases were observed in more than 26,000 additional births.[3] Gross and Benz[5] reported three cases occurring within one year in a hospital which has approximately 1,200 to 1,300 deliveries annually. In a review of 1,000 consecutive maternal deaths in North Carolina, four proved cases of amniotic fluid embolism were encountered. One death occurred in the North Carolina Baptist Hospital, the others elsewhere in the state.

Case Reports

CASE 1.—L. E. H., a 37-year-old white gravida ix, para iv, was admitted to the North Carolina Baptist Hospital on Jan. 9, 1951. Her last normal menstrual period had occurred on April 11, 1950, and her expected date of confinement was Jan. 14, 1951. This admission was the third during the present pregnancy. She was first admitted in the twentieth week because of a sudden episode of painless vaginal bleeding, with the loss of approximately 75 c.c. of blood. The patient was kept in the hospital for five days, during which time the bleeding completely ceased and roentgen studies indicated a midterm fetus in vertex presentation, with the placenta apparently implanted on the right anterolateral uterine wall. A sterile pelvic examination revealed a healthy cervix, and the presenting part was easily felt through the lower uterine segment. No soft tissue mass was palpable. Consequently, the patient was discharged. She had no further vaginal bleeding until the twenty-eighth week, when she began to have daily vaginal spotting. She was readmitted in the thirtieth week, and repeat roentgen examination showed a well-developed, single fetus in breech presentation; the placenta was not visualized. Pelvic examination again revealed no palpable placental tissue, and the patient was again discharged. On the final admission, in the thirty-ninth week, she was complaining of vague back pain. Daily vaginal spotting had been present since the thirty-first week.

The first pregnancy, in 1933, had ended in spontaneous abortion at eight weeks. The next four pregnancies were entirely uneventful. The sixth pregnancy, in 1945, resulted in abortion. Following this, a uterine suspension, partial oophorectomy, and appendectomy were performed. Thrombophlebitis of the left leg developed after this operation, and a left lumbar sympathectomy was performed. In September, 1945, a right nephropexy was performed because of hydronephrosis and nephroptosis. In March, 1946, the superficial femoral veins were ligated after an episode of recurrent thrombophlebitis. The seventh and eighth pregnancies resulted in spontaneous abortion.

Physical examination on the final hospital admission revealed a well-developed, middle-aged white woman in no distress. The blood pressure was 122/90, pulse 92, respirations 20, temperature 98.4° F. The lungs were clear to auscultation and percussion. The heart was not enlarged and there were no murmurs. The uterine fundus extended 27 cm. above the symphysis, and a single fetus was in the breech presentation. The fetal heart rate was 124 per minute. The presenting part was not engaged. There was slight edema of the left lower extremity.

Urinalysis was negative. The blood count showed a hemoglobin of 10 Gm., 3.9 million red blood cells and 10,100 white blood cells. The blood nonprotein nitrogen was 34 mg. per 100 c.c., blood urea nitrogen 9.4 mg. per 100 c.c., total serum proteins 5.6 Gm. per 100 c.c., with an albumin/globulin ratio of 2.9, and uric acid 3.6 mg. per 100 c.c. Urea clearance was 52 per cent average normal function. Kahn and Wassermann tests were negative.

Following admission the patient was kept at bed rest. She continued to have occasional mild abdominal pains, but did not go into labor and did not have significant vaginal bleeding. On the fourth hospital day she was given intravenous Pitocin in an effort to induce labor. A solution containing five minims of Pitocin in 500 c.c. of normal saline was used. Administration was begun at a rate of 20 drops per minute and gradually increased to 25 drops per minute. Mild to moderately intense contractions occurred every two to four minutes. Because there was poor relaxation of the uterus between contractions the Pitocin was discontinued after the patient had received 80 c.c. (0.6 minims). The patient was returned to her room and kept at bed rest for the next five days, during which time she had intermittent leakage of fluid per vaginam.

At 8:50 A.M., on the ninth hospital day, a second attempt was made to induce labor by using 5 minims of Pitocin in 500 c.c. of 5 per cent dextrose in water. The solution was started at a rate of 20 drops per minute. Almost immediately there occurred a tetanic uterine contraction which persisted for approximately eight minutes. During this time the fetal heart rate dropped to 80 per minute. The Pitocin was immediately discontinued, and it was estimated that the patient had received approximately 14 c.c. or 0.14 minims of Pitocin. Immediately after the tetanic uterine contraction the fetal heart rate returned to 130 per minute and was regular.

During the next two hours the patient had irregular uterine contractions with poor relaxation. Approximately two hours after the Pitocin had been started meconium was noted at the vaginal orifice. There was no bleeding. At 1:40 P.M. the fetal heart could no longer be heard. Rectal examination revealed the cervix to be dilated 1.5 cm., and the presenting part to be at station minus 4. At 5:00 P.M. a sterile pelvic examination revealed the cervix to be soft, 1.5 cm. long, and 2 cm. dilated. There was a moderate amount of meconium in the vagina, but no evidence of bleeding. The membranes were apparently ruptured and the fetal head could be easily palpated through a definite ring of thin "fibrous tissue" in the region of the internal os. Following the pelvic examination the patient continued to have strong uterine contractions with little relaxation. At 5:15 P.M. she was given 16 mg. of morphine sulfate subcutaneously, and 1,500 c.c. of 5 per cent dextrose in water and 500 c.c. of 5 per cent dextrose in saline intravenously.

At 7:00 P.M. the uterus was noted to be tense and tender; the blood pressure was recorded as 118/96 and the pulse rate as 100 per minute. At 8:00 P.M. the blood pressure was 120/90, the pulse 100. At 9:00 P.M. the patient was sleeping. At 10:20 P.M. she had

a chill, and her temperature was recorded as 99.2° F. At 11:00 P.M. the temperature was 101.4° F., the blood pressure 118/84, and the pulse rate 124 per minute. The patient vomited brownish fluid. She was given 16 mg. of morphine sulfate. At 11:30 P.M. the temperature was 102.6° F., and she continued to have nausea and vomiting. At 11:40 P.M. she complained of a sensation of smothering, and a malar flush was noted. A few fine râles were heard in the base of the right lung, and a slight cough had developed. At 11:45 P.M. the blood pressure was 80/50 and it was noted that the patient had become cyanotic. Oxygen was given. A blood transfusion was started slowly. At 12:05 A.M. on Jan. 18, 1951, the cyanosis deepened and respirations slowed. Oxygen was administered under positive pressure. Digitoxin and aminophylline were given intravenously, but the patient's blood pressure continued to fall and the pulse rate to rise. At 12:15 A.M. the patient was pronounced dead.

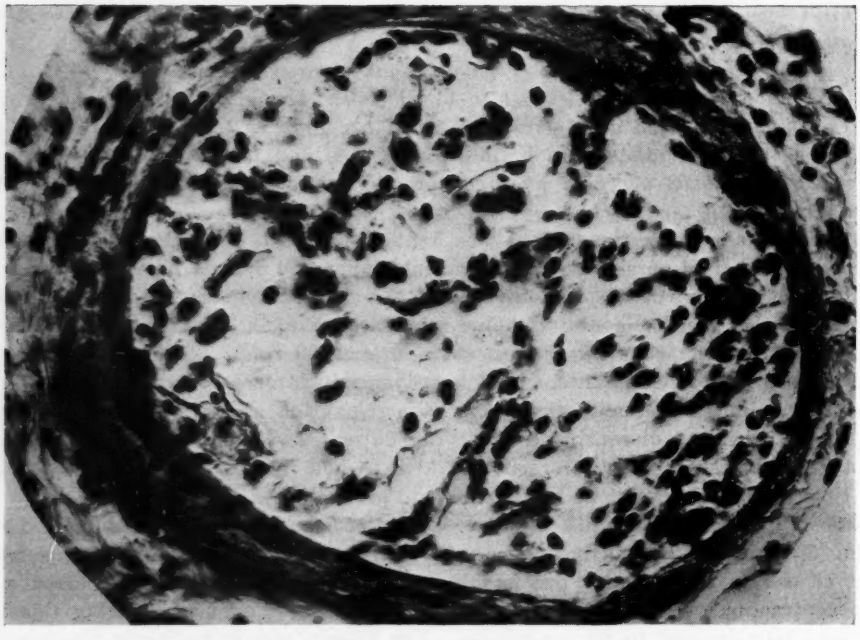

Fig. 1.—Microscopic section of the lung in Case 1 showing epithelial squamae, leukocytes, and fatty material in pulmonary arteriole.

At autopsy 500 c.c. of straw-colored fluid were found in the left pleural cavity and 250 c.c. of the same type of fluid in the right pleural cavity. The pericardial cavity contained 100 c.c. of clear fluid. The heart showed no abnormalities. The bronchi contained a moderate amount of frothy material. The left lung weighed 415 grams, and the right lung 650 grams; both lungs floated in water. The bronchi and large pulmonary vessels were thoroughly dissected, and no abnormalities were found. Exploration of the vena cava and iliac veins revealed no evidence of thrombi. The uterus measured 30 by 22 by 12 cm. A vertical incision was made in the anterior wall of the uterus and a well-developed male infant weighing 3,400 grams was removed. There was moderate molding of the fetal head. The placenta, which completely covered the internal os of the cervix, showed a 6 cm. opening through which the baby's head had penetrated. Approximately 500 c.c. of sanguineous fluid were found in the uterine cavity.

Microscopic examination of sections of the lung showed numerous small arteries and capillaries to be occluded by foreign material containing epithelial squamae (Fig. 1). There was moderate edema of the lungs, more marked on the right. When sections of

the uterus were examined microscopically, pink granular material containing epithelial squamae was found in some of the medium and smaller vessels (Fig. 2). Sections through the heart showed several of the smaller arterioles and capillaries to be plugged by typical amniotic squamae (Fig. 3).

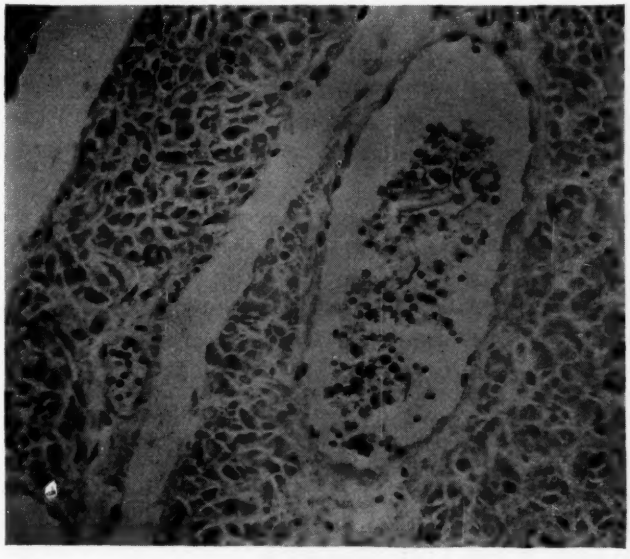

Fig. 2.—Microscopic section of uterine muscle showing packing of small artery by the particulate matter of amniotic fluid.

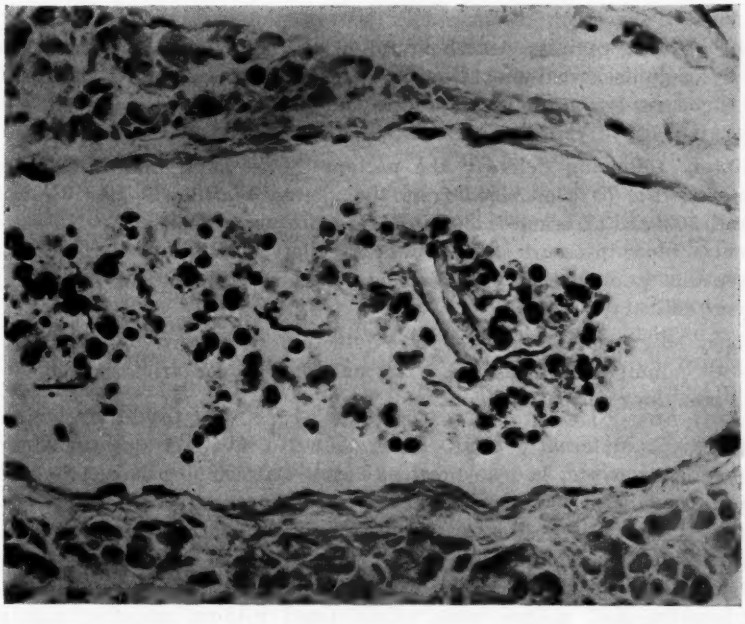

Fig. 3.—Microscopic section of the heart in Case 1. Note the amniotic debris including epithelial squamae in the small coronary vessel.

CASE 2.*—N. C. Maternal Welfare Files, Case No. 671. The patient was a 41-year-old white woman, gravida ii, para i, whose only child had been delivered 23 years previously

*The authors are indebted to Dr. L. N. Bell, Asheville, North Carolina for his kind permission to report this case.

without incident. This child, a daughter, had died suddenly during labor one year prior to the patient's death; an autopsy was not obtained. The patient had an uneventful prenatal course, and was not in labor when she was admitted to the hospital. Her blood pressure was 130/80, and there was a trace of albumin in the urine. Labor began spontaneously, and approximately one hour after the onset she began to have "violent" contractions. She suddenly complained of chest pain, exhibited marked dyspnea, and collapsed. She was given oxygen, Coramine, and plasma. Since examination revealed the cervix to be fully dilated, immediate low forceps delivery of a full-sized, stillborn infant was carried out under light anesthesia with cyclopropane, pentothal, and oxygen. There was no unusual bleeding. The patient's blood pressure never returned to its normal level, and she died 20 minutes after delivery.

Autopsy showed slight dilatation of the right ventricle. Grossly, the lungs appeared to be normal. Throughout the uterus there were seen small fibromyomas, the largest of which measured 4 by 3 by 1.5 cm. Microscopic studies of the lungs showed that all of the blood vessels were moderately dilated and many contained an abundance of mucoid and fatty material; the capillaries were packed with polymorphonuclear neutrophils.

CASE 3.*—N. C. Maternal Welfare Files, Case No. 525. The patient was a 37-year-old white woman, gravida ii, para i. She had mild uterine bleeding during the second month of the present pregnancy. She had no further difficulty until the last two months of pregnancy when considerable edema of the ankles developed. In the thirty-eighth week of pregnancy her blood pressure was 120/80 and the urine showed a trace of albumin. She was treated by salt restriction and cathartics. During the fortieth week her blood pressure was 130/90, and she was found to have 1 plus albuminuria.

The patient was admitted to the hospital and the membranes were ruptured artificially. Labor did not begin until approximately 40 hours later. Uterine contractions were "quite strong and closely spaced." Examination showed the cervix to be dilated 4 cm. and labor to be progressing rapidly. One hour following this examination the patient suddenly collapsed and her pulse was unobtainable. Plasma was begun. Examination revealed the patient to be ready for delivery, and a full-sized, stillborn infant was delivered by outlet forceps.

Immediately following delivery the patient "bled more than usual, estimated 400 c.c.," and a moderate ooze of blood from the vagina continued. She was given 3 pints of plasma and 500 c.c. of whole blood, and the uterus was packed. No record is given of the patient's blood pressure during delivery, but it is stated that her pulse did not become perceptible and she did not respond. She was pronounced dead approximately two hours after delivery.

At autopsy no gross abnormalities were detected. The positive findings on microscopic examination were limited to the lungs. The pulmonary capillaries showed mucus, foreign material, and numerous epithelial squamae.

CASE 4.—N. C. Maternal Welfare Files, Case No. 554. A 36-year-old white woman, gravida iv, para iii, who had had no previous obstetrical complications, was admitted to the hospital at term in labor. The membranes had ruptured shortly before admission and there had been no bleeding. Labor progressed normally, with contractions occurring every three to four minutes. After approximately four hours of labor the patient suddenly became cyanotic and went into coma. Her blood pressure fell and her pulse became extremely weak. Digifolin, Adrenalin, and oxygen were administered without response, and she died 20 minutes later undelivered.

No gross abnormalities were detected at autopsy. Microscopic examination of sections of the lungs showed numerous small pulmonary emboli made up of fatty material, mucus, and meconium.

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*The authors are indebted to the late Dr. Oren Moore, Charlotte, N. C., for his kind permission to report this and the following case.

Comment

Clinical and Pathologic Findings.—

Amniotic fluid embolism usually occurs in patients in the older age group who have borne two or more children. The prenatal course is usually uncomplicated. Frequently pregnancy has continued beyond term, and the fetus is often larger than average. Labor is most often characterized by strong or tetanic uterine contractions. The duration of labor, as a rule, is normal.

The initial symptoms and signs of amniotic fluid embolism are usually restlessness and chilly sensations. Vomiting is not uncommon. Unlike venous thrombotic embolism, pain in the chest is a rare complaint. Dyspnea and cyanosis become apparent and the patient presents a picture of shock, with lowered blood pressure and a rapid, weak pulse. Death usually follows in minutes or hours.

At autopsy the gross findings are not striking. Not infrequently uterine tears or an abnormal placental site is demonstrated. The diagnosis is made by the demonstration of amniotic fluid contents and meconium in the smaller pulmonary vessels. These elements may be present also in the vessels of other organs. In Case 1 they were demonstrated in the lungs, heart, and uterus.

In instances where permission for autopsy is not obtained, centrifugation of blood obtained from the right side of the heart may demonstrate a fluffy layer above the usual leukocytic cream.[5] Smears or paraffin sections of this material may demonstrate epithelial squamae.

Pathogenesis.—

The pathogenesis of this disease is not clearly understood. Landing[16] has pointed out that amniotic fluid usually gains entrance to the circulation through abnormally opened uterine vessels, either decidual or myometrial, such as found in placenta accreta, cesarean section, and ruptured uterus. Leary and Hertig[15] have found squamous cells within the placenta or its membranes in fourteen cases and state that careful examination of the placenta and membranes in cases of amniotic fluid embolism may shed light on the mechanism of entry of the fluid into the general circulation.

The abnormal bleeding noted in Case 3 occurred after the patient had collapsed and had been delivered. No lacerations were found at autopsy. In a review of 22 cases of amniotic fluid embolism, Weiner and Reid[17] noted that thirteen of fifteen patients who survived delivery had hemorrhagic manifestations prior to death. They suggested that, since the amount of mechanical blockage present in the lungs is not sufficient to cause death, amniotic fluid might contain an active principle responsible for the antepartum shock and postpartum hemorrhage. Studies by Weiner, Reid, and Roby[19] showed that amniotic fluid exerts a coagulant effect similar to that of thromboplastin, and that this effect is completely overcome *in vitro* by heparin. Howell,[20] Schneider,[21] and Fulton and Page[22] demonstrated that sublethal injections of thromboplastin into animals produce shock and increase the clotting time of the blood as a result of defibrination. Autopsies on the animals showed extensive arteriolar and capillary thrombi, particularly in the pulmonary system. Weiner and Reid[17] suggest that amniotic fluid might act in a similar manner—that is decrease fibrinogen by producing intravascular clotting. This defibrination of the blood might then lead to postpartum hemorrhage due to failure of the blood to clot normally.

In their original reports Steiner and Lushbaugh[1] attributed the sequelae of amniotic fluid embolism to anaphylactic shock resulting from the sudden deposition of amniotic contents in the pulmonary arterioles—the circulatory collapse, uterine hemorrhage, and other phenomena being secondary to the anaphylactic reaction. Eastman[23] re-emphasized this concept and called attention

to the earlier studies on anaphylactic shock by Hanzlik and Karsner.[24, 25] These authors, using guinea pigs, found that the intravenous injection of a wide variety of agents caused anaphylactoid reactions. The only difference between these reactions and true anaphylactic shock was the presence of thrombosis and embolism in the lungs of the animals following injection. They concluded that the anaphylactoid reactions were due to the embolism and thrombosis. Further studies, employing suspensions of charcoal particles and Fuller's earth, were then carried out. Symptoms identical to those of anaphylactic shock were produced and a marked decrease in blood coagulability was noted, particularly in the animals injected with Fuller's earth.

It is obvious that the sequence of events occurring when pulmonary arterioles and capillaries are blocked by the particulate matter of amniotic fluid is similar to that produced by injections of, for example, Fuller's earth. To date, the anaphylactoid theory appears to be the most likely explanation of the cause of death.

Prevention and Treatment.—

It appears that some of the deaths which have resulted from this entity could be classified as preventable. Certainly, induction of labor with Pituitrin should not be attempted in the older multipara. Evidence of sensitivity to small amounts of Pituitrin, manifested by strong uterine contractions, is sufficient warning to discontinue its use. Tetanic uterine contractions should be controlled by general anesthesia or by the judicious use of magnesium sulfate or magnesium gluconate.[26]

The fact that the diagnosis of placenta previa was not made in Case 1 led to absolute mismanagement. The fetal head had completely penetrated the placenta, and most certainly opened vessels through which amniotic fluid could gain entrance to the maternal circulation. The patient's abnormal response to the minute amount of Pitocin which she received initially should have discouraged its further use. The tetanic contraction which occurred at the beginning of the second induction was probably the initial insult which ultimately resulted in death.

Since the disease has never been recognized prior to death, no specific treatment has been tried. A diagnosis of amniotic fluid embolism should be considered whenever unexplained cyanosis and shock develop during labor, and oxygen should be administered at once. Reflex vascular spasm of the pulmonary vessels might be abolished with papaverine, and cardiac depressor reflexes from the lung could be controlled with atropine.[1] Should pulmonary edema develop, it should be actively treated. In the absence of definite evidence of internal or external bleeding, blood transfusion is probably not indicated. On the other hand, phlebotomy might be of value.

Weiner and Reid[17] have suggested that 50 to 75 mg. of heparin, administered intravenously, might be effective in decreasing the clotting activity of the amniotic fluid in the maternal vascular system. They suggest the use of fibrinogen in patients who survive the initial shock and subsequently develop hemorrhagic manifestations. This should be accompanied by blood transfusions to replace blood loss.

Summary

Four cases of sudden maternal death associated with amniotic fluid embolism are presented.

The present knowledge of the pathogenesis and treatment of this syndrome is discussed.

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2100 Princeton Avenue, Charlotte, N. C. (Dr. Sluder)

OBSTETRICAL VERSUS PEDIATRIC RESPONSIBILITY IN PREMATURITY

F. J. SCHOENECK, M.D., SYRACUSE, N. Y.

(From the Bureau of Maternal Hygiene, Department of Health)

A CRITICAL analysis of fetal and infant loss in the Syracuse area has caused us to modify some of our ideas concerning methods of reducing fetal wastage.

This study, a cooperative venture of the Department of Health of the City of Syracuse and the Maternal Welfare and Child Health Committees of the Onondaga County Medical Society, revealed that prematurity is the apparent leading cause of fetal loss. However, the remarkably high incidence of associated obstetrical complications must be considered in evaluating the complete picture.

The study showed that the major corrective effort was aimed predominantly at saving premature babies after they were born. We acknowledge, unequivocally, the importance of this approach. However, there is a real doubt in our mind that continued improvement of pediatric care, alone, can offer a major solution to the problem. It is our feeling that the real solution of prematurity, as well as most other factors involved in fetal wastage, lies in the direction of correcting its obstetrical aspects.

Material

The data presented, herewith, are primarily concerned with 24,666 live births and 405 stillbirths which occurred in the city of Syracuse during the three-year period, 1949-1951. Prematurity was determined by weight—any fetus weighing 2,500 grams (5 pounds, 8 ounces) or less was considered as premature. However, any fetus weighing 500 grams or less was classified as an abortus. Seven and five-tenths per cent of the live births were of premature (501-2,500 grams) infants.

Three principal approaches were considered in analyzing the situation. The first consists of data obtained from questionnaires sent to the attending physician (obstetrician) in all instances of deaths occurring in premature infants.

In addition, all stillbirth certificates for the period were analyzed. The second approach concerns the time and weight factors as they apply to fatalities in premature infants. The third factor used entails an artificial classification of primary obstetrical versus primary pediatric factors responsible for fatalities in prematures.

It should be pointed out that obstetrical and pediatric factors are involved rather than the responsibility of the obstetrical or pediatric specialties, per se.

Causes of Prematurity

Table I shows the causes of prematurity in 299 infant deaths according to data from questionnaires submitted to the attending obstetrician. There

were 365 deaths associated with prematurity according to official records in Syracuse during the three-year period, 1949-1951. Questionnaires were sent out within a few weeks of each infant's death, asking, among other things, the physician's opinion as to the cause of premature labor. Two hundred ninety-nine responses were received, so these data are based on 82 per cent of the actual deaths. It should be emphasized that the causes given are those of premature labor and not necessarily the causes of death.

Many factors are of necessity involved in obtaining a true picture of fetal wastage in prematurity. Twenty-three of the deaths occurred in fetuses weighing 500 grams or less, and, according to our local criteria, these are classified as abortuses. In addition, there were thirty-three induced labors for various obstetrical indications. Twenty, in the latter category, were cesarean sections and eleven induced by other methods. It is certainly doubtful, when the causes of premature labor are considered, if these induced labors can be included. It would be necessary, to be completely technical, to exclude 56 (18.6 per cent) cases from this group since they were either abortions or artifically induced premature labors.

TABLE I. CAUSES OF PREMATURITY, SYRACUSE, N. Y., 1949-1951

299 Cases (Fatalities)

CAUSE	DEATHS OF PREMATURE INFANTS, 500 TO 2,500 GRAMS NO.	ABORTUSES UNDER 500 GRAMS NO.	INDUCED LABOR		TOTAL NUMBER	PERCENTAGE
			CAESAREAN	OTHER		
Placenta.—						
Abruptio	25	2	0	0	27	9.0
Previa	14	0	5	3	22	7.3
Other	14	3	1	0	18	6.0
Multiple pregnancy	33	2	0	0	35	11.7
Maternal Disease.—						
Toxemia	3	0	7	4	14	4.6
Diabetes	1	1	0	0	2	
Malnutrition	6	0	0	0	6	2.0
Nephritis	1	0	1	0	2	
Syphilis	2	0	0	0	2	
Central nervous system	0	0	3	0	3	
Infectious diseases	6	0	0	0	6	2.0
Maternal Accident.—						
Overexertion	7	2	0	0	9	3.0
Accident (trauma)	4	0	0	0	4	
Coitus	2	0	0	0	2	
Obesity	1	0	0	0	1	
Auto trip	3	0	0	0	3	
Other	6	0	0	0	6	2.0
Uterus.—						
Cervical pathology	4	0	0	0	4	
Fibroids	1	1	0	0	2	
Fundus (other)	3	0	0	0	3	
Criminal abortion	0	1	0	0	1	
Chronic abortion	9	4	0	0	13	4.3
Congenital anomalies	19	0	1	1	21	7.0
Erythroblastosis	1	0	1	3	5	1.6
Undetermined	80	7	1	0	88	29.4
Total	245	23	20	11	299	

Analysis of Table I shows placental factors to be associated as possible causes of prematurity in 22.3 per cent of the cases; abruptio placentae accounting for 9.0 per cent, placenta previa for 7.3 per cent, and other placental conditions for the remaining 6 per cent.

Multiple pregnancy is the apparent leading single factor (11.7 per cent). Other statistically appreciable causes are the various toxemias of pregnancy (4.6 per cent), chronic abortion (4.3 per cent), and congenital anomalies (7.0 per cent). It should be noted at this point that, in actual cause of death, major congenital anomalies are lethal in about 10 per cent of both infant deaths and stillbirths.

The other factors listed are responsible for prematurity in a lesser degree.

The attending obstetrician could offer no obvious explanation for the onset of premature labor in 29.4 per cent of the cases. One-third (33.0 per cent) of this group had unexplained spontaneous rupture of membranes prior to the onset of labor.

It is interesting to note that if we had analyzed this same group of cases merely from the data available on death certificates, the cause of prematurity would be given as undetermined in 80 per cent. This would seem to point out the importance of considering the source of data in evaluating a problem such as this.

TABLE II. STILLBIRTHS, SYRACUSE, N. Y., 1949-1951, CAUSES
(Data from Stillbirth Certificates)

CAUSE	ABORTUS (UNDER 500 GRAMS)	PREMATURE (501-2,500 GRAMS)	MATURE (2,501 GRAMS +)	INDUCED LABOR		TOTAL	
				MECHANICAL	CESAREAN		
Placenta.—							
Abruptio	8	52	16	0	1	77	
Previa	0	3	3	2	1	9	(26%)
Other	2	11	4	1	1	19	
Cord complications	8	18	48	0	1	75	(19%)
Multiple pregnancy	1	4	0	0	0	5	
Maternal Disease.—							
Toxemia	3	10	8	7	1	29	(7%)
Diabetes	0	4	1	0	1	6	
Nephritis	0	6	2	0	0	8	
Syphilis	0	1	1	0	0	2	
Infectious diseases	0	4	1	0	0	5	
Maternal Accident.—							
Overexertion	0	1	0	0	0	1	
Accident (trauma)	0	3	0	0	0	3	
Poisoning	0	1	0	0	0	1	
Other	1	0	0	0	0	1	
Uterus.—							
Cervical pathology	1	1	0	0	0	2	
Fibroids	0	0	0	0	1	1	
Fundus (other)	1	1	0	0	2	4	
Criminal abortion	0	1	0	0	0	1	
Missed abortion	0	2	0	0	0	2	
Congenital anomalies	4	19	8	1	0	32	(8%)
Erythroblastosis	4	15	15	2	1	37	(9%)
Undetermined	9	29	34	1	6	79	(19%)
Total	42	186	141	14	16	399	

It would seem fair to state that an analysis of Table I reveals that, in the majority of these fatalities in prematures, the prematurity was associated with an obstetrical complication. We question, therefore, that oft-repeated statement that prematurity per se is the leading cause of fetal and infant deaths.

Table II presents an analysis of 399 stillbirths which occurred in Syracuse during the three-year period 1949-1951. Data were inconclusive on six additional stillbirths (total 405) and are not included. Fifty-seven per cent of all stillborn infants were premature; however, of these, 42, almost 10 per cent,

weighed 500 grams or less and are classified as abortuses. An additional 30 cases (8 per cent) occurred in artificially induced labors, 16 cesareans and 14 induced by other methods.

In a study of this group, from the point of view of causes of prematurity, it again became apparent that the majority of cases are associated with obstetrical complications. Placental factors are prominent, as they were in the infant-death group. Two additional factors become evident, namely, umbilical cord complications and erythroblastosis.

We point out the readily accepted observation that most of the stillbirths are associated with obstetrical complications.

Time and Weight Factors

The breakdown on the time of death in the group of premature fatalities, excluding those classified as abortuses, is as follows:

Died during the first 24 hours	69.5%
Died—25 hours to 7 days	19.8%
Died—8 days to 1 year	10.7%

It will be seen that more than two-thirds of these fatalities in prematures occurred in the first twenty-four hours of life. It would seem doubtful that any improvement in pediatric care could materially influence this group. Many fatalities in the second group occurred during the second twenty-four hours and, in general, the same statement would probably apply to the majority of these deaths. The third group—8 days to 1 year—probably could be influenced by improvement in pediatric care, but cannot afford any major reduction in mortality rate.

An analysis of the weight factor, in premature deaths during the three-year period 1949-1951, reveals the following data:

WEIGHT	NUMBER DELIVERED	DIED	FATALITY RATE
Under 500 grams (Abortus)	30	30	100.0%
501-1,000 grams	106	104	97.0%
1,001-1,500 grams	164	102	62.2%
1,501-2,000 grams	381	64	16.8%
2,001-2,500 grams	1,201	70	5.8%

These data point out the generally accepted thesis that the smaller the premature, the less is the chance of survival. It can be seen that a premature must have a birth weight of 1,500 grams (3 pounds, 5 ounces) in order to have a reasonably good chance of survival.

If we combine the time factor (approximately 70 per cent of the prematures die within the first twenty-four hours) and the weight factor (the fatality rate of prematures from 501-1,500 grams is 76 per cent), it would seem to emphasize that the final solution cannot be accomplished by improved pediatric care of prematures after they are born.

Pediatric Versus Obstetrical Responsibility

On the basis of data presented above, we have created an artificial classification of obstetrical versus pediatric responsibility in premature fatalities.

We classify obstetrical factors as being of primary responsibility if any of the following three criteria is present:

1. Birth weight 3 pounds, 8 ounces or less.
2. Major obstetrical complication associated with prematurity, regardless of weight (under 2,500 grams).

3. Major congenital anomaly associated with prematurity, regardless of weight (under 2,500 grams).

Pediatric aspects are given primary responsibility if the premature weighs more than 3 pounds, 8 ounces and the fetus and pregnancy are otherwise normal.

On these criteria, the primary responsibility for the premature fatalities in Syracuse from 1949-1951 is as follows:

Primary obstetrical factors	85.0%
Primary pediatric factors	15.0%

The criteria, which we have arbitrarily established, are naturally controversial. However, if it is kept in mind that our objective, in this grouping, is to establish primary factors of responsibility in fetal and infant loss so that corrective measures may be realistically faced, the point may then be emphasized that the major solution must be centered in correcting the obstetrical aspects of the problem.

Comment

There is unquestionably a growing trend toward increased attention to fetal salvage. The maternal mortality problem, from a practical point of view, has been reduced to a most satisfactory level in most areas of the United States. It would seem natural, therefore, to face the very real problem of fetal and infant loss.

Our studies in this field would seem to indicate fetal salvage as essentially an obstetrical problem. We are not alone in our thinking on this subject. Calkins[1] states that reduction in fetal mortality may be achieved by (1) improved obstetric care which would reduce the incidence of premature deliveries, (2) improvement in the management of labor, and (3) increased knowledge of placental pathology. Pomerance and Steiner[2] state that the major factors in incidence of premature births are complications of pregnancy. Lock and Major[3] have pointed out the importance of proper analgesia and anesthesia as factors in fetal survival. Simpson and Geppert[4] in a recent review of the subject state, "Ninety per cent of [this] fetal loss is attributed to prenatal and natal causes." Many other authors could be quoted to corroborate this type of thinking.

Nevertheless, a critical analysis of the recent literature reveals that the usual recommendations for the prevention of prematurity consist of good care during the prenatal period, labor, and delivery. These have been general aims since obstetrics was recognized as a specialty. Vitamins, especially vitamin E, have occasionally been employed as a specific measure. The present relatively widespread employment of endocrine products during pregnancy has not produced constant results. The very fact that we find it necessary to deal with the fetal and infant wastage problem is strong evidence that the presently employed methods of preventing prematurity are not satisfactory. We believe that prematurity and the other factors relating to fetal wastage present the "big" obstetrical challenge of the day.

The ultimate solution of this problem would seem to resolve itself into several specific approaches:

1. Basic Research.—A considered analysis of the causes of prematurity seems to emphasize the need for basic research on several aspects of obstetrical complications from the primary consideration of fetal wastage.

Perhaps the outstanding single factor is placental pathology. This subject is currently receiving a great deal of attention and real progress in its control could potentially reduce fetal wastage by 25 per cent.

One-third of the unexplained premature labors in our series were precipitated by spontaneous rupture of the membranes. Why do membranes rupture in this manner and can anything be done to prevent it? This would seem a fertile investigative field.

Recent studies on faulty germ plasm and faulty imbedding facilities of the endometrium suggest intriguing possibilities.

These are but a few examples of the potential basic research approaches that must play a leading role in any real solution of the problem of fetal wastage.

2. Clinicopathological Conferences on Fetal Deaths.—Statistical studies may well present the problem of fetal salvage in its true light. There seems to be no stronger method, however, of creating interest and promoting the corrective needs of the problem than analysis of individual fatalities by a combined obstetric-pediatric-pathologic group in clinical conference.

This approach, patterned after the highly successful maternal mortality committee technique, has a most important place in any fetal salvage program. The fetal and infant mortality conference is being employed in many centers at present, but it should be adopted in every hospital and medical center in the country.

3. Better Usage of Present Obstetrical Knowledge.—There is considerable present-day obstetrical knowledge that, potentially, could be put to better usage for the specific purpose of reducing fetal mortality.

An example of this type of thinking concerns multiple pregnancy, one of the prominently associated factors in prematurity. If multiple pregnancy is kept in mind, it could be suspected in the first trimester of pregnancy by astute pelvic examination. Suspicion that the uterus is even slightly larger than it should be, would suggest a quantitative pregnancy test. It has been amply demonstrated that the chorionic gonadotrophic level is higher in multiple than in single pregnancy. If the clinical suspicion of multiple pregnancy is corroborated by laboratory evidence, prophylactic hormonal therapy, such as is presently used in chronic abortion, could be employed and might prove to be efficacious.

Another possibility concerns maternal infections in the first trimester of pregnancy. The relationship of German measles to congenital anomalies is reasonably well understood. There is evidence[5] that other infectious diseases, not necessarily of virus etiology, may similarly affect the fetus. More intensive antibiotic therapy for relatively innocuous maternal infections during the first trimester could conceivably influence this picture. The possibility of protecting the fetus in these situations by active immunization, or even hormonal therapy, might be worthy of consideration.

The so-called conservative management of placenta previa, whereby pregnancy is prolonged, despite hemorrhage that would ordinarily indicate termination of pregnancy, in the sole interests of the fetus, is an example of this type of approach already in use.

Naturally, such a policy could not be advocated unless conditions were ideal for the mother's protection. This must be a basic principle—we certainly cannot chance an increase in maternal mortality to accomplish the purpose of reduced fetal wastage.

The demonstration of Hughes, Van Ness, and Lloyd[6] of the role of faulty nutritional factors, especially of glycogen, in the endometrium as potentials in sterility and infertility problems opens a new field of approach. These workers have been able to correct these faulty factors by the use of stimulative estrogen therapy prior to conception and have obtained subsequent normal pregnancies in sufficient numbers to warrant consideration of this method.

Their use of chorionic gonadotrophic and pregnandiol levels during early pregnancy as a guide to hormonal therapy, also, merits consideration.

The examples cited may serve as a stimulus to a concerted effort of putting presently available knowledge to wider usage for the specific purpose of reducing fetal wastage.

4. Previous Obstetrical Histories.—The significance of chronic abortion, recurrent premature labors, and hereditary patterns of congenital anomalies is fairly well understood. Histories of this type, naturally, place the physician on guard for possible difficulties in the future.

We have come to consider the term "bad pregnancy" as connoting abortion, premature labor, congenital anomaly, or major obstetrical complication, or any combination of these factors, as a definite entity. Our preliminary studies suggest that all reproductive histories will fall into one of four categories.

The first of these groupings includes the vast majority—at least 90 per cent—of natural reproductive histories. All pregnancies, for practical purposes, are normal. The occasional "bad pregnancy" usually can be explained by some obvious incidental cause, such as, for example, severe trauma precipitating an abortion. The second group, in contrast, shows practically all pregnancies to be "bad," a normal living child being the exception rather than the rule. A third grouping shows a pattern of two or three normal pregnancies, following which practically all pregnancies are "bad." The fourth and smallest group, demonstrates a pattern of two or three "bad pregnancies," following which practically all pregnancies are normal.

In addition, preliminary studies suggest that if the first pregnancy terminates as an abortion or premature labor, the possibility of the second pregnancy being completely normal is only about 50 per cent, whereas, if the first pregnancy is completely normal, the chances of the second pregnancy being normal are roughly 90 per cent.

We are presently trying to confirm these early impressions by more extensive studies.

While it is conceded that modern obstetrics entails due consideration to past obstetrical history, a more detailed evaluation from the specific viewpoint of fetal salvage might prove of value.

5. Preconceptional Diagnosis and Treatment.—The potential of anticipating "bad pregnancies," coupled with the work of Hughes and his group (Department of Obstetrics, New York State University Medical College at Syracuse) whereby they are apparently able to influence nutritional factors in faulty endometria, led to the establishment of a "Preconceptional Treatment Clinic" in Syracuse. Couples with histories of premature labors, congenitally defective offspring, and chronic abortion are accepted. Complete studies of both the wife and husband are undertaken. General physical examinations, with special attention to the reproductive and endocrine systems are made. Extensive laboratory data are obtained and due consideration given to nutritional, environmental, and sociological factors. Any abnormal conditions are duly evaluated and treated. If and when such abnormalities are corrected, these patients are instructed to conceive. The mother, when she becomes pregnant, is followed in conjunction with her private physician or in a special prenatal clinic.

The "Preconceptional Treatment Clinic" is conducted by the Obstetrical Department of the New York State University College of Medicine at Syracuse in cooperation with the Syracuse and New York State Departments of Health. The clinic has been in operation since September, 1950, and, while it is obviously much too early even to consider conclusions, it may be stated that the results obtained to date have been sufficiently encouraging to warrant continued work along this line as a specific approach toward fetal salvage.

Summary

Evidence is presented to suggest that any major reduction in fetal wastage will necessitate correction of the obstetrical aspects of the problem. Continuing improvement of the pediatric care of prematurely born infants is, of course, essential, and will undoubtedly be instrumental in fetal salvage, but, in the majority of instances, the odds are too great to expect pediatric care alone to accomplish salvage.

Obstetrical complications play a major role in fetal wastage. Several methods of accomplishing fetal salvage, as it pertains to the obstetrical aspects, are suggested.

One conclusion seems obvious. The multiplicity of factors involved demonstrates clearly that many approaches must be employed. It is certainly doubtful that any single medical center can solve a sufficient number of these aspects to influence the over-all situation materially. It is suggested that a single national agency, such as, perhaps, the American Committee on Maternal Welfare, Inc., could coordinate the various aspects of the program. A single national agency could guard against repetition and assure reasonable inclusion of all important aspects. Basic and clinical research already in progress in many centers could undoubtedly be modified to include the fetal wastage aspects of the work. It is suggested that an organized approach, on a national scale, could accomplish more, and in a shorter time, than if the various medical centers approach this problem in a purely independent manner.

The object of this presentation is to stimulate concerted attention to a problem the medical profession readily accepts as important. If we can accept "fetal salvage" as the "big" obstetrical challenge of the day, we may anticipate that cooperative effort will accomplish similar results to those obtained in the truly phenomenal reduction of maternal mortality.

I wish to acknowledge the encouragement and cooperation, in this work, of C. A. Sargent, M.D., Commissioner of Health, Syracuse, N. Y., and E. C. Hughes, M.D., Director of the Bureau of Maternal Hygiene.

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PROPHYLAXIS OF POSTPARTUM URINARY RETENTION

Preliminary Report

A. R. Fleming, M.D., Baltimore, Md.

(From the Department of Obstetrics, Mercy Hospital)

THE incidence of urinary retention following delivery has been reported as 13.8 per cent,[1] while in the postoperative period it occurs in as many as half the cases. This is particularly true in gynecological or lower abdominal surgery.[2] The occurrence of urinary retention commits the already tired, nervous, and distressed postoperative or postpartum patient to the discomforts of catheterization, which in turn may further aggravate the condition or prolong hospitalization by causing genitourinary tract infection. This is apparently not the only sequela following catheterization or bladder distention, for, as stated by Woodruff and Te Linde,[2] "In our experience in female urological conditions we have been struck with the frequency with which patients date their illnesses from trouble in emptying the bladder after operation." Aside from the discomfort to the patient, the possibility of infection and/or urological disturbances, another factor which militates against catheterization is the present-day shortage of nursing personnel.

There are many points of contention concerning the exact nature and physiology of micturition. From the practical aspect one may say that urination is under the dual control of the voluntary and autonomic nervous systems, which means a normal individual may suppress or initiate micturition at will. The desire to void is usually first noted at a bladder volume of between 200 and 300 c.c.; this volume initiates the micturition reflex which consists of a strong contraction of the detrusor muscle accompanied by relaxation of the internal sphincter and followed by opening of the external sphincter. This reflex may be voluntarily suppressed until the bladder volume is much larger, or, on the other hand, it may be initiated by contraction of the abdominal muscles when the contents of the bladder are below that volume ordinarily required to give rise to the urge to void.[3]

In the postpartum patient the entire physiology of the bladder is disarranged as evidenced by the cystometric and cystoscopic evaluations in Bennetts and Judd's[4] excellent investigation. Their study showed that in only 19 of 116 cases did the bladder show any evidence of ecchymosis, such as might have been expected from direct trauma. In 86.2 per cent of these patients cystometric evaluations showed no severely painful desire to void at a bladder volume of 1,000 c.c. They concluded that, as a class, the postpartum bladder resembles the hypotonic type of bladder in its greatly diminished muscular tone, decreased sensitivity, and markedly increased capacity. Normal physiology is gradually re-established during the postpartum period and by the end of the third week the bladder has returned to an almost normal state.[5]

The deranged bladder physiology following delivery readily lends itself to infection. Of the cases reported by Buxbaum and Udesky[6] 45 per cent showed residual urine, while in another series[7] 80 per cent were demonstrated to have a bacteriuria on the third postpartum day. Prather[8] noted that the

patients showing residual urine also showed temperatures of 99 degrees or above. Despite all of these factors the incidence of genitourinary tract infection in the puerperium is amazingly low. McLane's[9] figures show that the incidence of pyelonephritis in the postpartum patient is only 0.5 per cent, and Taussig[10] reported the incidence of postpartum cystitis as 3.8 per cent. The inference is that the diagnosis of genitourinary tract infection is frequenty overlooked or that the bladder is very resistant to infection in its puerperal state.

There is apparently no single factor leading to postpartum urinary retention. Anesthesia, analgesia, length of labor and/or the various stages of labor, care of the bladder during labor, and trauma to the bladder itself or to its innervation all must contribute to the reported 13.8 per cent incidence. Previous studies suggest that urinary retention occurs as frequently with general anesthesia as with spinal anesthesia.[1] According to some authors[8, 11] the tendency to retention increases in proportion to the length of labor; the type of delivery, on the other hand, has little to do with the occurrence of urinary retention. The type of episiotomy and the pain often following this procedure have also been postulated as factors affecting micturition.[5] Psychic factors must also add their contribution to the somatic possibilities; increasing anxiety resulting from the inability to void may reflexly inhibit micturition and thus the offended becomes the offender.[12, 13]

Many different treatments have been used to avoid postoperative and postpartum catheterization. Some of these include: (1) Bladder instillation of: Mercurochrome,[1, 2, 15] silver proteinate[14] acriflavine,[15] boroglycerine,[2] and air.[2] (2) Parenteral administration of: Prostigmine,[6, 15] Mecholyl,[2] Doryl,[15] furfuryl compounds,[16, 17] thiamine hydrochloride,[11] and Urecholine.[18] (3) Oral administration of Urecholine, Mecholyl,[2] and furfuryl compounds.[16, 17]

In this study Urecholine (the urethane of beta methylcholine chloride) was used in the treatment and prophylaxis of postpartum urinary retention. Urecholine is a parasympathetic stimulant acting as a chemical mediator in stimulating the receptor cells of smooth muscle. This action is in contrast to the physostigmine group of parasympathetic stimulants, which includes the synthetic compound, Prostigmine. These drugs have no direct action on smooth muscle, but act through the inhibition of cholinesterase.[19, 20]

Lee[21] has shown by cystograms that Urecholine increases the tone and contractility of the normal bladder and the bladder showing hypotonic dysfunction. Urecholine then affects the postpartum bladder much as oxytocics act on the postpartum uterus to help re-establish tone and aid in the process of involution.

Urecholine has been reported useful in the clinical treatment of acute and chronic urinary retention,[18, 21, 22] postoperative intestinal distention,[19] gastric retention following vagotomy,[23, 24] and it has been suggested as a treatment for megacolon.[25]

The contraindications to the use of Urecholine are based on theoretical considerations.[26] In the present study there were only four patients in whom significant side reactions occurred. Two of the patients showed a pulse rate below 60 per minute while on the prophylactic dose, but the drug was not discontinued, the third patient became nauseated while taking 30 mg. (6 tablets) four times daily and the drug was discontinued. It was thought that this last effect was due to the bulk of the drug rather than to its pharmacological activity. The fourth patient showed the reported flushing, perspiring, and faintness following subcutaneous administration of 2.5 mg. and the drug was discontinued. Transitory mild flushing with perspiration occasionally occurred with the subcutaneous dosage, but in only one instance was it deemed necessary to discontinue the use of the drug because of this. None of the patients in this study required the use of the antidote, atropine. It is felt that Urecholine should not be used

in any condition in which increased gastric motility or intestinal peristalsis would be detrimental to the patient's welfare; nor in cases of vesical neck obstruction, bladder surgery, or pregnancy.[18, 26]

Material

A group of 767 multiparas and primiparas were observed for postpartum urinary retention; 129 of these patients were placed on a prophylactic dose of Urecholine in an effort to avoid urinary retention, while the remaining 638 were subject to its use only if urinary retention occurred.

All patients were on a routine catheterization order varying from 8 to 12 hours and an effort was made to give the patient every opportunity to void spontaneously before each catheterization. To this end routine nursing procedures were used and when necessary the patients were allowed out of bed before catheterization or treatment.

The prohylactic dosage used varied from 15 to 30 mg. The patients received an initial dose upon return to their rooms and this was repeated every 4 to 6 hours for the first 24 hours.

Except as noted in the two patients above, there were no changes in the blood pressure, pulse, and respirations which were checked every four hours in all of the patients in the prophylactic group.

The treatment most frequently used was an initial oral dose of 20 mg. of Urecholine which was repeated in one hour if the patient did not micturate. After the second dose another hour was allowed to elapse; if the patient failed to void during this time she was catheterized. A lesser number received a subcutaneous dose of Urecholine, the amount used varying from 2.5 to 5 mg., which was repeated in 30 minutes if necessary. If the patient failed to void after one to two doses, she was catheterized 30 to 40 minutes after the last dose.

As shown in Table I, in the group receiving Urecholine prophylactically the incidence of postpartum urinary retention was 2.3 per cent as compared with 11.4 per cent in the group not receiving the prophylactic dose.

TABLE I

	PROPHYLACTIC GROUP		TREATMENT GROUP	
	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Total patients	129	100.0	638	100.0
Incidence of retention	3	2.3	73	11.4

Two of the three cases considered as failures in the prophylactic group were voiding in 300 to 400 c.c. amounts prior to catheterization, but were still distended. Not included as failures are the following six cases: Four patients required supplemental subcutaneous Urecholine along with the oral prophylactic dose, before voiding adequately. Two other patients were catheterized when the eight-hour order was up; of these, one had no desire to void and no evidence of distention; upon catheterization only 150 c.c. of urine were obtained. The second had a desire to void, but did not appear distended; upon catheterization no urine was obtained.

These last two cases serve to emphasize that, before any catheterization in the postpartum patient, there should be a history of recent, adequate fluid intake. Sedation, anesthesia, nausea, vomiting, and fatigue all contribute to poor fluid intake and dehydration immediately following delivery. This, associated with the increased capacity and diminished sensation of the postpartum bladder, makes it unwise to use distention and desire to void as the sole indications for catheterization.

In the group receiving Urecholine only as treatment, 73, or 11.4 per cent, showed acute urinary retention (Table II). For various reasons ten of these patients received no Urecholine. The remaining 63 patients were given the treatment dose in an effort to relieve bladder distention without catheterization. This was successful in 46 per cent of these patients.

TABLE II

	TREATMENT GROUP	
	NUMBER OF PATIENTS	PERCENTAGE
Total number of patients	638	
Incidence of retention	73	11.4
Treatment dose successful	29	46.0
Treatment dose failed	34	54.0

Nine of the 34 patients listed as failures in the treatment group received inadequate dosage or were catheterized before permitting the alotted one hour for Urecholine to exert its full effect. Another factor to consider is that the vast majority of these patients were treated by oral dosage instead of subcutaneous Urecholine as is recommended for acute urinary retention.

TABLE III

	PROPHYLACTIC GROUP		TREATMENT GROUP	
Average length of labor	9 hours 30 minutes		11 hours 41 minutes	
TOTAL LENGTH OF LABOR	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Under 7 hours	54	41.9	18	24.7
7 to 10 hours	25	19.4	18	24.7
10 to 24 hours	43	33.3	33	45.2
24 hours or above	3	2.3	4	5.5
Unknown	4	3.1	0	0.0
Total	129	100.0	73	100.1

In Table III it will be noted that the average length of labor in the 73 patients receiving the treatment dose was two hours and eleven minutes longer than in the prophylactic group. Furthermore, 75.4 per cent of the treatment group had a total length of labor of over 7 hours as compared to 55 per cent in the prophylactic group. Table IV shows that the percentages and times of the second stage of labor for the two groups show a similar relationship. This may be a factor influencing the results and making the prophylactic use of the Urecholine seem better than it actually is.

TABLE IV

	PROPHYLACTIC GROUP		TREATMENT GROUP	
SECOND STAGE OF LABOR	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
2 hours or under	114	88.4	52	71.2
2 hours or above	11	8.5	21	28.8
Unknown	4	3.1	0	0.0
Total	129	100.0	73	100.0

The routine sedation used at this hospital consists of: Seconal, 0.2 Gm. (3 grains), orally and Demerol, 100 mg., with scopolamine, 0.4 mg. (1/150 grain), given intramuscularly or one-half intravenously. In Table V it is shown that 84.6 per cent in the prophylactic group and 60.2 per cent in the

treatment group received routine sedation or less. There does not appear to be any significant relationship between the amount of sedation and the incidence of urinary retention in this study.

TABLE V

	PROPHYLACTIC GROUP		TREATMENT GROUP	
ANALGESIA RECEIVED	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
No sedation	16	12.4	2	2.7
Less than routine	34	26.4	12	16.4
Routine (IM)	26	20.2	10	13.7
Routine (½ IV)	33	25.6	20	27.4
More than routine	20	15.5	29	39.7
Total	129	100.1	73	99.9

The incidence of operative delivery (Table VI) is also much higher in the 73 patients requiring treatment (treatment group) than in the prophylactic group. The significance of this cannot be properly appraised until more data are collected from groups showing less variation than the two groups represented in this study.

TABLE VI

	PROPHYLACTIC GROUP		TREATMENT GROUP	
Total number of patients	129		73	
DELIVERY STATISTICS	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Spontaneous delivery	46	35.7	8	11
Low forceps	73	56.6	55	75.3
Midforceps	5	3.9	5	6.8
Breech	5	3.9	5	6.8
Episiotomies	88	68.2	65	89.0
Various complications	29	22.5	16	21.9

The statistics in Table VII show that the majority of all of these patients received spinal (saddle block) anesthesia.

TABLE VII

	PROPHYLACTIC GROUP		TREATMENT GROUP	
Total number of patients	129		73	
TYPE ANESTHESIA	NUMBER OF PATIENTS	PERCENTAGE	NUMBER OF PATIENTS	PERCENTAGE
Spinal (saddle block)	96	74.4	62	84.9
Inhalation	26	20.2	5	6.8
Local	0	0	1	1.4
Combined	5	3.9	3	4.1
Unknown	2	1.6	2	2.7
Total	129	100.1	73	99.9

Summary

1. A brief résumé of the physiology of the normal and postpartum bladder is given. The incidence of postpartum urinary retention in 638 patients of this study was 11.4 per cent.

2. Urecholine chloride (the urethane of beta methylcholine chloride) was used prophylactically in an effort to avoid urinary retention and therapeutically to avoid catheterization.

a. Urecholine apparently reduced the incidence of postpartum urinary retention from a reported 13.8 per cent[1] to 2.3 per cent when used prophylactically in 129 patients.

b. When used therapeutically Urecholine was successful in relieving acute urinary retention in 46 per cent of 73 cases.

3. Labor, type of delivery, analgesia and anesthesia records show a fairly normal distribution for both groups, but do not show any predominant, common factor in either group that might aid in forecasting postpartum urinary retention.

4. It is believed that Urecholine's apparent effectiveness and freedom from side reactions merit further study and use in the prophylaxis of postpartum urinary retention.

Conclusions

The statistical tables for both groups show a fairly normal distribution in the types of delivery, lengths of labor, analgesia and anesthesia such as is comparable to those in the service of any obstetrical department. The incidence of urinary retention in the 638 patients not receiving Urecholine prophylactically was 11.4 per cent.

Urecholine chloride (the urethane of beta methylcholine chloride)* apparently reduced the incidence of urinary retention from a reported 13.8 per cent[1] to 2.3 per cent when used prophylactically. When used therapeutically to prevent catheterization it was effective in 46 per cent of the cases in this study. It is felt that Urecholine would have been even more effective therapeutically if it had been given subcutaneously in a larger number of these patients. Though the two groups do not compare well it is believed that Urecholine's effectiveness and freedom from side effects prophylactically are sufficient to merit further study and wider usage in the prevention of postpartum urinary retention. This study is being continued and it is hoped that a more comprehensive report can be made during the coming year.

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RAPID ESTIMATION OF PLASMA FIBRINOGEN CONCENTRATION AND ITS USE AS A GUIDE TO THERAPY OF INTRAVASCULAR DEFIBRINATION*†

CHARLES L. SCHNEIDER, PH.D., M.D., DETROIT, MICH.

(From the Department of Physiology and Pharmacology and the Department of Obstetrics and Gynecology, Wayne University College of Medicine, and from Herman Kiefer Hospital)

THE need for a rapid and simple assay for fibrinopenia is increasing because of increased clinical recognition of acute, active defibrination. Defibrination is important not because of the frequency of its occurrence but because of the desperate gravity to the rare individual in whom it may occur.

The assay method presented below is designed not for precision but for use by the clinician himself to obtain an approximate evaluation *on short notice* whenever needed.

Defibrination of the circulating blood is encountered as an infrequent but severe complication of late pregnancy.[1, 2, 4, 7, 8, 11-17, 20, 21] This is usually in the presence of clinically recognized abruptio placentae. In certain remaining obstetrical cases complicated by defibrination, the question of whether abruptio placentae had occurred sometimes arises from later reconsideration of the histories.[13] Defibrination may be encountered also in transfusion reactions and conceivably to a significant degree in severe burns and crush injuries.

In obstetrics the question may be posed whether extensive defibrination is essentially always the result of abruptio placentae.[13] It may also be wondered whether the initial "accidental" retroplacental hemorrhage itself may be progressively aggravated if defibrination of the circulation does ensue.[2, 11] Rarely, a generalized and spontaneous hemorrhagic diathesis develops[5, 6] and this appears to be associated with the acquired afibrinogenemia.[7] More frequently, the fibrinopenia of abruptio placentae results merely in a *potential* hemorrhagic diathesis.[11, 17] Although there may be little or no spontaneous bleeding, the condition is nevertheless a hazardous one for it may contribute, should any bleeding point develop, to a state of *manifest* hemorrhage.[2, 7, 8, 11-17, 20] Because of the fibrinopenia, there may be significant bleeding from even a minor laceration at delivery. Similarly, surgery, whether perineal or abdominal, performed for the purposes of delivery may, in the presence of defibrination, result in severe hemorrhage. An occasional patient may bleed uncontrollably despite application of customary surgical techniques for hemostasis. Bleeding has been observed to continue from the vascular bed of the exposed tissues, and about both arms of sutures placed to control the bleeding.[12] Despite the most diverse concepts as to the origin of the fibrinopenia, there seems to be agreement that,

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in severe fibrinopenia, adequate hemostasis is best achieved by restoring the circulating coagulation mechanism itself.[2, 7, 8, 11-17, 20, 21]

It is imperative to be able to evaluate[11] the degree of fibrinopenia *before* delivery or *before* a surgical procedure which may be required as an emergency measure.[1, 11, 12] Only thus is it possible to anticipate adequately need of replenishment of the coagulation mechanism. This knowledge is of value largely in proportion to its availability in advance of the crucial need. In the author's experience, current laboratory practice usually requires hours for a report of a fibrinogen concentration, or because of essential economic limitations upon "round the clock" service, there is likely to be a delay until the following workday of the laboratory. Unfortunately, a laboratory assay or report, available several hours or a few days after the crucial time of hemorrhage, is too late to be of service in making decisions of treatment. The method suggested here may be performed by the resident staff or by the consultant while clinical decisions are in progress of formulation. Hence, the results may aid in the decision as to therapy and thereby may aid in reducing still further the now small remainder of maternal mortality.

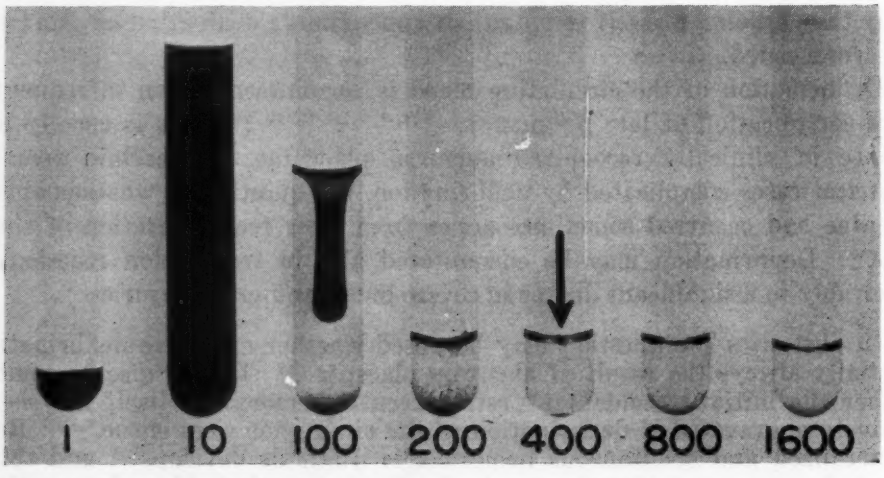

Fig. 1.—Serial dilutions of whole blood to determine fibrin titer during a normal pregnancy near term. The highest dilution, 400, in which there is a visible clot is by definition the titer. A series of dilutions modified from that shown here is recommended for evaluation of fibrinopenia. See text.

Method

An approximate estimation of the fibrinogen concentration in the venous blood is obtained in terms of a fibrin titer. The assay is designed so that it can be carried out with equipment available to the obstetrical ward officer.

The result with a simple dilution series of whole blood is shown in Fig. 1. The highest dilution in which visible coagulation of fibrin occurs is by definition, a "fibrin titer." The titer is quoted in terms of dilution of the contained plasma.

Materials

Ordinary 12 by 100 mm. glass test tubes such as are used in collecting blood for serology are arranged 8 in a row. One row of tubes is used for dilution of the patient's whole blood as described below. The second row is used for similar dilution of the blood of a control obstetrical patient who does not have abruptio placentae. Additional rows may be used for follow-up titers of the patient with abruptio.

Diluent.—Ringer's solution such as is used for intravenous administration is a satisfactory diluent because it supplies an appropriate concentration of the needed calcium ions for coagulation in the assay dilution series. If Ringer's solution is not available, a satisfactory diluent can be made up as needed by mixing 9 parts of 0.85 per cent sodium chloride solution which is available on the ward, with 1 part of M/40 calcium chloride, which is usually available as a reagent for prothrombin assays in the hospital laboratory.

It is pertinent to note that spuriously low titers can be caused by acidity of the diluent. When saline was made up in "de-ionized" water, the acidity was so great as to overcome the buffering capacity of the blood in its higher dilutions, and thus to lower the pH below the critical level for coagulation. Fortunately, the saline used in the hospital ward or laboratory is ordinarily of a higher pH. Saline, in different hospitals used in the actual assays on control patients and on patients with abruptio placentae, was found to be satisfactory.

Thrombin.—If it is desired to use thrombin, a convenient source of reagent is bovine Thrombin Topical of Parke, Davis & Co.; this is likely to be available in the operating room as a hemostatic agent. When needed, the contents of one vial can be dissolved in saline to give 100 units per milliliter. Better still, if a stable stock solution is desired, 50 per cent glycerol may be used as solvent to make up a solution of 200 units per milliliter; when stored in the refrigerator, this reagent will maintain adequate activity for many months.[18]

Procedure

Dilutions.—First, place 3 ml. of the diluent in the second tube of each row of tubes, 4 ml. in the third tube, and 1 ml. in each of the remaining tubes.

Venous blood is then drawn from the patient into a syringe of small diameter (a 1 ml., or ½ ml. tuberculin syringe or insulin syringe is of small enough diameter to be admitted deeply into the dilution tubes for mixing and sampling) and is dispensed and diluted, at once, directly from the syringe, at the bedside, into the series of assay tubes in the following manner: An undiluted control sample is set aside by discharging all but 0.5 ml. of the blood from the syringe into the first tube. The remaining 0.5 ml. of whole blood is then discharged into the second tube and is thoroughly mixed with the 3 ml. of diluent already in it. With the same syringe, 1 ml. of this mixture is carried over to the next tube. The remaining twofold dilutions are accomplished by carrying over a 1 ml. aliquot serially from each tube to the next. Assuming a hematocrit of approximately 0.35, the resultant dilutions of the plasma component are: 1, 10, 50, 100, 200, 400, 800, 1600.

With care, the original syringe may be used to make the dilutions. In each successive dilution, the mixing may be accomplished by repeated aspiration and ejection from the syringe. During this mixing process, the plunger of the syringe itself may be removed and immersed into the diluted mixture once before the final refluxing; this reduces the risk of excessive "carry-over" from one dilution to the next, particularly during the first dilutions.

Readings.—The rack of tubes is allowed to stand at room temperature, preferably without shaking, until the time of reading. Each tube is then tilted back and forth to find the highest dilution in which a visible coagulum has formed. As can be seen from Fig. 1 in the dilutions near the end point, the fibrin may contract to a minute clot, or, indeed, if there has been shaking, may accumulate directly as a minute clot. One hour is a suitable time for reading. After two hours or longer, a reading at a one-tube higher dilution may be found.

Occasionally, however, fibrinolysis[7, 11, 20, 21] occurs. Lysis of clots of whole blood or of diluted blood within intervals up to 24 hours has been used to

demonstrate fibrinolysis.[7, 11, 20, 21] In the case of Table II, the delicate clots that formed in the higher dilutions were observed to disintegrate within 1 to 2 hours. This is an unusually rapid lysis; sometimes lysis is not evident. This demonstrates, however, that to delay the time of reading may result, upon occasion, in a lower rather than a higher apparent fibrin titer.

Controls.—Because of the infrequency with which one may use the fibrin titer assay, it is desirable to perform a control titer at the same time, on the blood of one or more normally pregnant women, near term or just delivered, to provide a check on the technique. When several such comparisons are made, it is found that a difference of one tube is not necessarily significant.

A control sample from a nonpregnant individual may be used if it is kept in mind that the fibrinogen content is approximately 250 mg. per cent rather than the usual 500 mg. per cent that is more characteristic of normal term pregnancy[1]; still higher levels may occur in toxemia of pregnancy.[1]

Alternate Procedure With Added Thrombin

In the above method, coagulation of fibrinogen depends upon the conversion of prothrombin in the diluted blood to thrombin. Under special conditions to be discussed below, but not ordinarily to be encountered in the acute phase of abruptio placentae, uncertainties may arise because of inadequate formation of thrombin, to give quantitative conversion of fibrinogen to fibrin. These uncertainties may be largely avoided by adding thrombin itself as a reagent in the assay.

On an obstetrical service where more than an occasional case of abruptio placentae occurs, it may be worth while to keep a stock solution of thrombin in glycerine on hand in the refrigerator to facilitate performing the assay in this manner.

A dilution series of venous blood is made up as in the procedure above. To each tube are then added 10 units or more of thrombin per milliliter of diluted blood (0.1 ml. of thrombin solution from a syringe or pipette is adequate, or one drop can be added from a medicine dropper); this is mixed in at once by tilting the tubes back and forth. Coagulation occurs within a few seconds and is complete within a few minutes.

Results

Validity of Assay.—Assays for evaluation of the method were carried out on blood from different sources. The results are described below.

Defibrinated Dogs.—The defibrination was brought about by injection of thromboplastin intravenously.[8-10] Results from one experimental animal before and after defibrination are given in Table I.

For comparison of the fibrin titers, fibrinogen determinations by a standard assay method[19] are included in Table I. Plasma separated from the successive collections of blood from the dog were frozen until the time of assay. Aliquots of thawed plasma were thirty times diluted, buffered, and recalcified; thrombin was added to facilitate coagulation; the clot was then wound out, washed, and digested. The fibrin digest was assayed in terms of tyrosine yield.[19]

It is clear from the data of Table I that the assay performed with simple dilution of the blood in the presence of added calcium ions as in the method above may give an approximate demonstration of the degree of fibrinopenia. In additional experiments in which there was partial defibrination, the fibrin titers were of intermediate magnitude.

The titers corresponded roughly to the concentrations in milligrams per cent of fibrinogen in the plasma, but the correlation is not close enough to permit calibration in those terms. The apparent minimum concentration of

fibrinogen that could be detected in this way varied considerably to either side of 10 mg. per cent.

As seen in Table I, the titer when the assay is performed with added thrombin is sometimes one tube higher than without added thrombin. A similar one tube higher titer is sometimes obtained when thrombin is added in the dilution series of blood of human abruptio placentae.

TABLE I. FIBRIN TITERS AND FIBRINOGEN DETERMINATIONS ON A DOG, BEFORE AND AFTER DEFIBRINATION BY INJECTION OF THROMBOPLASTIN INTRAVENOUSLY

	CONTROL SPECIMEN		HOURS AFTER INTRAVENOUS INJECTION OF A LARGE DOSE OF THROMBOPLASTIN		
	FIRST	SECOND	1	2	4
Fibrinogen concentration, mg. per cent plasma	230	240	11	9	8
Fibrin Titer.—					
Saline dilution	10	10	1	0	1
Saline dilution with added calcium chloride	200	200	0	0	0
Same dilution with added thrombin	400	400	0	0	0

Normal Human Pregnancy.—A titer of 800 was common in normally pregnant women near term; as is characteristic of any "titer" assay, there was variation. The variations can usually be limited to one tube in either direction by observation of careful technique of dilution.

Abruptio Placentae.—Although clinically the cases of abruptio placentae that were used in the present evaluation were severe, yet defibrination was not usually as severe as in the experimental animal of Table I. The levels in the clinically severe cases usually were below 100 mg. per cent of plasma, a level which is sometimes arbitrarily considered as a limiting concentration for adequate hemostasis.

TABLE II. FIBRIN TITERS AND FIBRINOGEN DETERMINATIONS ON THE BLOOD OF A WOMAN WITH SPONTANEOUS FIBRINOPENIA, DURING ABRUPTIO PLACENTAE (HKH No. 97778)

	CONTROL CASE (NORMAL PREGNANCY)	HOURS AFTER INITIATION OF SPONTANEOUS ABRUPTIO PLACENTAE					
		5	10	11	14	34	60
Fibrinogen, mg. per cent	510	60	60	60	110	390	780
Fibrin titer	800			50-100 (During cesarean)	200	200	

Data from a sample case are presented in Table II. The titer of fibrin indicated that at the time of surgery the circulating fibrinogen was of the order of one-eighth, or less, of that found late in normal pregnancy. This was believed to be low enough to present a potential hazard of hemorrhage, and it was believed that therapeutic support of the circulating coagulation mechanism should be recommended.

Modifying Conditions.—Occasionally, to provide a basis for comparison, it becomes desirable to perform a fibrin titer on previously collected specimens of blood or plasma, e.g., on samples drawn for other studies earlier in the progress of the abruptio, but which may be still available for testing.

A fibrin titer may be determined on whole citrated or oxalated blood or plasma, the diluent restoring sufficient calcium ions to support coagulation. However, especially after abruptio placentae, the apparent titer may decrease rapidly with increasing duration of storage of the sample, even in the re-

frigerator, and there is the possibility of obtaining exaggeratedly low titers from such stored specimens. The use of added thrombin in the assay largely obviates this error unless fibrinolysis has occurred meanwhile.

Similarly, a critically needed specimen collected early in the clinical course of the abruptio placentae may be available in "double oxalate," i.e., in a mixture of ammonium and potassium oxalates, such as is used in hematologic studies. Such specimens are adequate if added thrombin is used to cause the coagulation in the fibrin titer assay, but are inadequate for a titer depending upon spontaneous coagulation, because the ammonium ions interfere markedly with the activation of prothrombin to thrombin, and hence with the quantitative formation of fibrin.

The data from the case of Table II illustrate still another way in which an exaggeratedly low value in the fibrin titer assay may be avoided by use of thrombin in the assay. In Table II, the fibrin titer was low during convalescence, 34 hours after the abruptio. This low titer resulted despite a relatively adequate restoration of fibrinogen; it coincided with delayed restoration of the plasma Ac-globulin[4] and is presumed to be the result of deficiency of this accelerator of coagulation.

It is noteworthy that venous blood drawn after acute intravascular coagulation in the experimental dogs but not control specimens drawn beforehand tended to form a minute clot in the test tube. The same may be observed in plasma from venous blood during abruptio placentae. Neither citrate nor oxalate was always wholly adequate to suppress formation of some fibrin within the stored plasma, and there was not infrequently a minute fibrin clot after thawing the stored, frozen samples. For this reason, the corresponding fibrinogen concentrations such as those recorded in Tables I and II may be somewhat in error in the direction of low values.

Comment

The technique outlined above serves to distinguish during abruptio placentae the patient with critically low fibrinogen levels but about whom there may be uncertainty by clinical evaluation alone. The usefulness of this method may be compared with the usefulness of other methods.

The coagulation time is of little assistance because, although it gives an estimate of the rate of coagulation, this may bear no necessary relationship to the amount of fibrinogen available for coagulation. As an example, a specimen of blood collected from the patient of Table II at the time of surgery coagulated within less than five minutes, although the fibrinogen concentration was later found to have been only 60 mg. per cent. Clearly, the clotting time gave an index of efficiency of coagulation enzymes, but not a measure of available coagulable material.

Similarly, in our experience, the apparent strength of the clot, or fragmentation of the clot, may be unreliable as an index of submarginal fibrinogen concentration, although such methods may be useful in evaluation of extreme degrees of defibrination.[20] As an example, in the case of Table II, the appearance of the test tube clot led the obstetrician who was carrying out the cesarean section to believe that the coagulability was still essentially within adequate limits. In another case, in which the patient was equally depleted of fibrinogen, the opinions were reversed; the same obstetrician felt that the quality of the clot was markedly defective while the author believed, incorrectly, that it appeared adequate.

The fibrin titer assay outlined above, when run in comparison with normal control specimens, appears to be suitable for the detection of fibrinogen depletion when this approaches the critical levels of approximately 100 mg. per cent or less.

Under special conditions which are considered under "Results" certain extraneous factors may be introduced and some of these tend to result in exaggeratedly low titers. These are not ordinarily present during the acute phase of clinically recognized abruptio placentae, and spuriously low values are not usually a problem in its management. The assay can be facilitated, and if the assay is used under unusual conditions the possibility of exaggeratedly low titers may be minimized by using thrombin to cause the coagulation in the fibrin titer assay.

The fibrin titer method has not been evaluated for study of possible defibrination in disorders other than abruptio. If used for the investigation of possible defibrination in transfusion reactions, burns, crush injuries, or amniotic fluid embolism, it is to be recommended that the thrombin be added in the dilution series. The added thrombin, together with the dilutions, would be particularly desirable if there were marked depletion of accelerators of coagulation, or release of inhibitors of coagulation in the disorder under consideration.

Summary

A fibrin titer assay has been devised for the rapid evaluation of fibrinopenia. This method was evaluated first on blood from experimental animals made fibrinopenic by inducing intravascular coagulation. The method was also evaluated on whole blood from normal and abnormal human pregnancies, including blood from patients with severe, spontaneous defibrination arising during abruptio placentae.

In abruptio placentae, the method can be used to obtain an approximate estimate of the degree of fibrinopenia, rapidly enough to provide a guide for prompt clinical therapy and management. Titers below 100 are suggestive of fibrinogen concentrations below 100 mg. per cent of plasma.

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MENSTRUAL ARRHYTHMIAS: ORAL ESTROGEN AND PROGESTERONE THERAPY

WILLIAM BICKERS, M.D., RICHMOND, VA.

MENSTRUATION is a bloody discharge associated with necrosis of the uterine mucosa, recurring, in the absence of pregnancy, at intervals of three and one-half to five weeks in certain primates.[1] The purpose and function of menstrual bleeding are unknown. The bleeding follows sudden regression of the endometrium in the wake of abrupt withdrawal of ovarian steroid support.[2] When estrogen and progesterone support to the endometrium is slowly withdrawn, no bleeding occurs.[3] Denial of estrogen and progesterone support not only induces endometrial shedding, but provides at least one stimulus by way of which the anterior lobe is stimulated to secrete its follicle-stimulating hormone (F. S. H.) for the growth and maturation of the ovarian follicle in the ensuing cycle. It is upon this premise that the rationale of cyclic estrogen and progesterone treatment in the anovulatory cycle is based.

Endocrine Cycle

Estrogen.—Early in the postmenstrual period several Graafian follicles are started on their way to maturity under the impulse of the follicle-stimulating hormone (F. S. H.) of the anterior pituitary.* A peak of estrogen production from the maturing follicle occurs in the immediate preovulatory period and then a level is established which is maintained during the functional life of the corpus luteum. Estrogen is the essential hormone for growth and vascularization of the endometrium and its withdrawal is the prime factor in initiating menstruation.[4] This is true despite the fact that progesterone is produced by the corpus luteum in amounts nearly eight hundred times that of estrogen. A 50 per cent drop in estrogen blood level is followed by endometrial shedding.

Progesterone.—During the period of full corpus luteum activity, the human ovary produces something over 10.0 Gm. of progesterone daily. Whereas the progesterone level may reach 5.0 mg. in 100 c.c. of blood, the estrogen level never exceeds 6.0 micrograms in the same blood volume.[5]

There is little relationship between the plasma level of the ovarian steroids and the onset of menstruation, it is the quantitative change in steroid levels which effects the endometrial regression.

Progesterone has for its major functions the induction of secretory activity in the endometrial glands and vascularization of the periglandular arterial bed. It has been said that the small amount of progesterone present before ovulation may act synergistically with estrogen to cause release of the luteinizing hormone (L. H.) and luteotropic hormone (L. T. H.) for the induction of ovulation, but this has not been confirmed.[6, 7]

Endocrine Interrelation.—The interaction of ovarian and pituitary hormones provides a highly coordinated effort, influenced by the nervous system, to produce a cycle of events terminating in menstruation. A deficiency in either estrogen or progesterone is followed by a compensating rise in the secretion of pituitary gonadotropins. The cycle is instituted by the fall in available estrogen

*This review of present-day concepts of menstrual physiology was aided by frequent reference to "The Physiology of Menstruation" published in *Seminar*, Sharpe & Dohme, February, 1951.

and progesterone which is followed by pituitary awakening. It has been suggested that a high level of estrogen during pregnancy may be nature's way of preventing growth and maturation of the new ova. In general it may be said that the interrelation is a reciprocal one between the ovarian steroids and the F. S. H. and L. S. H. hormones of the anterior pituitary.[8]

Endometrial Cycle

The menstrual cycle is the gestational cycle in miniature.

Endometrial growth is the product of vascular growth which in turn depends upon the endocrine environment. The cycle may be considered as one of four distinct phases: (1) the rest phase which persists for some four to five days after complete re-epithelization of the depleted menstrual endometrium; (2) a primary growth phase which lasts until the mid-cycle; (3) a secondary period of growth under stimulus of progesterone from the corpus luteum; (4) a period of regression which is an essential precursor to menstruation following directly upon the withdrawal of vascular support in the endometrium.[2]

During the first growth phase estrogen proliferates the endometrial glands from stumps left from the preceding cycle. Straight tubular glands develop in a compact stroma with relatively few blood vessels. Following ovulation the second growth phase under the impetus of corpus luteum secretions, estrogen and progesterone, occurs and the glands become longer, their lumina wider, and the stroma more highly vascularized. Growth and differentiation of the glands proceed at a rapid rate until the distended cytoplasm of the epithelial cells lining the tubular glands crowd upon one another forcing the epithelium into folds which bulge into the gland lumen. The stroma becomes highly edematous and some of the stroma cells may even assume a pseudo decidual appearance. The vascular and lymphatic beds are dilated and the whole tissue is hyperemic and congested. This is the prenidatory endometrium fabricated under the stimulus of the ovarian steroids, estrogen and progesterone. Involution of the corpus luteum is accompanied by withdrawal of the estrogen and progesterone support. Shrinkage of the tissue ensues rapidly, foci of necrosis appear, and depletion of the functional layer of the endometrium follows.[9]

Vascular Cycle of the Endometrium.—The human endometrium is one of a very few mammalian tissues which has a specialized type of coiled spiral arteries. These arteries originate in the myometrium just beneath the endometrium, traverse the basal layer of the endometrium, and terminate in the capillaries about the endometrial glands in the subepithelial space. These arteries are directly under the influence of the ovarian steroids.

Within two hours after the subcutaneous injection of estrogen, the endometrial transplant in the cornea of the rabbit's eye will show evidence of vascular dilatation. Progesterone effects its growth-stimulating properties by capillary dilatation in the basket network of capillaries about the glands. When estrogen and progesterone support is withdrawn the volume of blood passing through the capillary bed in the stroma and periglandular area diminishes. Edema subsides, buckling of the spiral end arteries ensues, and a slowing of the blood flow through the capillaries is apparent. This stasis is responsible for the areas of focal necrosis in the endometrium which ultimately slough, permitting jet hemorrhage from the nearest artery. This is the bleeding of menstruation.[10]

Denial of ovarian steroid support to the vascular bed in the endometrium is associated with a catabolic tissue toxin which favors endometrial necrosis.[11, 12]

Bleeding of menstruation stops spontaneously when all necrotic tissue has been shed. Such necrotic tissue is the source of the necrosin. A clot forms in the vessel plugging the coiled artery and regeneration of arteries and veins occurs promptly along with epithelial regeneration under the stimulus of the estrogens.

Menstrual Arrhythmias and Their Physiologic Basis

On the basis of at least one report it can be said that approximately 45 per cent of all patients between the ages of 17 and 40 years who consult a gynecologist in private practice have as their chief complaint some disturbance in interval, amount, or duration of menstruation. In such a group 12 per cent will complain of amenorrhea or oligomenorrhea and 23 per cent of hypermenorrhea or polymenorrhea as their major complaint.[13] It seems paradoxical, but the evidence is overwhelming to the effect that amenorrhea and polymenorrhea have essentially the same pathologic physiology. Endometrial biopsies on large numbers of patients in both groups indicate that ovulation failure is the underlying disturbance. It is presumed that the endometrium is capable of normal response to ovarian steroid stimulation. Uterine bleeding can be stopped by the administration of either estrogen or progesterone and induced by the withdrawal of either.

Failure of ovulation and persistence of the unruptured follicle results in prolonged estrogenic stimulation uncomplemented by progesterone.

Functional bleeding as well as amenorrhea may occur from any type of proliferative endometrium, atrophic or cystic glandular hyperplasia.[14, 15, 16] In most cases the ovarian deficit responsible for the menstrual arrythmia is not intrinsic within the ovary, but is secondary to pituitary failure. Evidence to support this belief is based on the fact that patients with obvious ovarian failure associated with amenorrhea or functional uterine bleeding usually show no elevation of the F. S. H. This stands in contrast to those patients in the menopause where ovarian failure is followed by a reciprocal elevation of the F. S. H. production from the anterior lobe of the pituitary.

Rationale of Therapy.—Induction of cyclic uterine bleeding in patients with amenorrhea and in patients with functional uterine bleeding has been accomplished by the cyclic administration of estrogen and progesterone.[17, 18] Not only is the cycle of bleeding established but the therapy is more than substitutional in that it may be followed by a return to pituitary-ovarian functional adequacy. The best indicator of such adequacy is cyclic uterine bleeding from a progestational endometrium. Uterine bleeding according to plan can be established in the majority of patients suffering from any type of functional menstrual arrhythmia while under treatment.

Treatment of Menstrual Arrhythmias

Out of the wealth of published experience several principles seem to assert themselves.[19] First, cyclic steroid therapy of the menstrual irregularities seems to be well established.[20] Treatment programs may differ but the basic concept is generally held that the administration of estrogen throughout the proposed cycle supplemented by progesterone during the last five to ten days of estrogen administration usually establishes cyclic bleeding. Estrogen in relatively large doses is recommended on the fifth through the twenty-fourth days or the fifteenth through the twenty-fourth days of the cycle to be supplemented by progesterone on the twentieth through twenty-fourth days of the cycle. Recommended doses of these hormones vary somewhat, but essentially most investigators agree that the estrogen should be given in a dose sufficient to suppress gonadotropic secretion and this means in

the case of stilbestrol 3.0 mg. to 6.0 mg. daily or in the case of the mixed natural estrogens 3.75 mg. to 7.5 mg. daily. Progesterone intramuscularly is usually recommended in a dose of 10.0 mg. to 20.0 mg. daily.

A second principle of therapy that is lately emerging is a preference for oral over the injectable hormones.[21] On the basis of animal experiments, it was long held that oral progesterone was either not absorbed or not metabolized by the human female. One of the conversion products of progesterone, anhydrohydroxy progesterone, was recommended for oral use. It has been shown in recent studies that pure crystalline progesterone is absorbed and metabolized by the human being.[22] Whereas intramuscularly administered progesterone induces a progestational endometrium in the estrogen-primed woman after five daily doses of 10.0 mg., a comparable response from the orally administered progesterone requires 80.0 mg. daily for five days.

Third, preference for repeated cycles of ten-day steroid therapy on the fifteenth through the twenty-four days of the cycle in contrast to the shorter treatment periods is gaining ascendency. The incidence of relapse after the establishment of three consecutive cycles in which treatment is administered from the fifteenth to the twenty-fourth day seems to be less than when the treatment schedule is compressed into fewer days. Steroids do not stimulate the endometrium in the sense that we usually understand the word "stimulate." They induce tissue metabolic changes. Reorientation of pituitary-ovarian endometrial physiology involves a time factor no less important than the hormone employed.

The fourth principle of therapy which is gaining ascendency is the preference for the natural hormones or those chemically related.[23] In the delicate pituitary-ovarian endometrial balance where so many unknowns exist it is reasonable to presume that those hormones which most closely simulate the natural secretions of the body are more likely to favor a return to normal physiology.

Clinical Study

Amenorrhea.—In a group of patients with functional amenorrhea the validity of these therapeutic principles has been tested. A tablet containing 1.0 mg. of the mixed natural estrogens and 30.0 mg. of crystalline progesterone (Cyclogesterin)* has been employed. It was found after some study that 3.0 mg. of the mixed natural estrogens and 90.0 mg. of progesterone administered daily over a period of five days was almost invariably followed by withdrawal bleeding. This dose was adequate to induce uterine bleeding and minimum progestational changes even in castrate patients. These patients are always the most difficult to treat because there is no base of endogenously produced steroids upon which to build.

More recently a group of sixteen amenorrheic patients have been treated by daily administration of three tablets (each tablet containing the mixed natural estrogens, 1.0 mg., and progesterone, 30.0 mg.), beginning on the fifteenth day of the proposed cycle. The period of amenorrhea in these patients varied from four weeks to eight months. Two of the patients in this series were amenorrheic following a bilateral oophorectomy in which the uterus had been left in place. This treatment program was followed over thirty-nine cycles in this group of patients and a fair to excellent bleeding response occurred in thirty-four of those cycles. There were twenty-two endometrial biopsies done within the first forty-eight hours of induced bleeding and the progestational response varied from one plus to four plus in them.

*Cyclogesterin (Upjohn) was the product used. Tablets contained mixed natural estrogens, 1.0 mg. and progesterone, 30.0 mg.

These observations would seem to indicate that the optimal dose schedule in the treatment of amenorrhea and oligomenorrhea is 3.0 mg. daily of the mixed natural estrogens and 90.0 mg. daily of crystalline progesterone in divided doses over a period of ten days beginning on the fifteenth day of the proposed cycle. If this cyclic treatment be repeated over three consecutive cycles one may expect cyclic uterine bleeding while under treatment. Upon discontinuing treatment about 50 per cent of patients may be expected to menstruate cyclically for indeterminate periods.

Patients with amenorrhea of more than six months' duration and the amenorrhea following castration are the most refractory to treatment and the majority of them will relapse after discontinuing therapy. In those patients with oligomenorrhea and secondary amenorrhea of less than three months' duration the relapse rate is low. Some patients in whom a normal cycle is established may continue to menstruate from a progestational endometrium indicating that in a small group ovulation salvage has been achieved.

Functional Uterine Bleeding.—

Patients with polymenorrhea associated with ovulation failure have been studied to evaluate the combined oral estrogen-progesterone therapy. A group of twenty-two patients with functional uterine bleeding have been subjected to treatment with a tablet containing 1.0 mg. of the mixed natural estrogens and 30.0 mg. of progesterone. This tablet has been administered three times daily for a period of ten days.

Endometrial biopsies were obtained on eighteen of the twenty-two patients during one of their prolonged bleeding episodes and a proliferative phase endometrium was found in all. Cystic glandular hyperplasia of the endometrium was found in eight patients, a persistent proliferative phase endometrium in seven patients, and the atrophic proliferative phase endometrium in three patients. It is obvious that functional uterine bleeding, although occurring almost invariably from a proliferative phase endometrium, may be associated with any degree of atrophy or hyperplasia. Treatment was instituted in all twenty-two patients as soon as the diagnosis of functional uterine bleeding was made.

Bleeding was reduced but never controlled in two of these patients on the dose schedule described. Seventeen patients stopped bleeding within four days of beginning therapy and hemostasis was maintained during the treatment period. Four patients ceased to bleed on the fifth day of therapy. Bleeding recurred on an average of six and one-half days after discontinuing the ten-day treatment course. This withdrawal bleeding was usually rather free and lasted four to eight days. Therapy was resumed on the fifteenth day of the proposed cycle and this was accomplished in twenty patients. They received the mixed natural estrogens and crystalline progesterone orally over a period of ten days, beginning on the fifteenth day from the first bleeding episode and withdrawal bleeding occurred in all patients between the fifth and seventh days after discontinuing the second treatment cycle. Cyclic bleeding according to plan was established in fifteen of the twenty-two patients over a period of three consecutive bleeding cycles. In these fifteen patients, twelve were followed during three months after treatment and in five the functional uterine bleeding recurred.

Endometrial biopsies were taken on six patients during their bleeding episodes in the first month after completing therapy and a progestational endometrium of two plus was found in two patients, three plus in one patient, and four plus in four patients.

From these observations a satisfactory plan for the management of functional uterine bleeding seems to be the administration of the mixed natural

estrogens in a dose of 1.0 mg. and crystalline progesterone in a dose of 30.0 mg. three times daily for ten days. The succeeding treatment course is instituted on the fifteenth day of the induced bleeding episode and in like manner the third treatment cycle. In other words, the ovarian steroid therapy is given from the fifteenth to the twenty-fifth day over three consecutive treatment cycles. Relapse to functional uterine bleeding after three months of such therapy did not exceed 50 per cent in a six months' follow-up.

Conclusions

1. The physiology of the endometrial and vascular cycles has been reviewed in relationship to the pituitary-ovarian cycle. Newer knowledge related to the ovarian steroids and their effect upon vascular activity is discussed.

2. The mixed natural estrogens combined with progesterone (in a dose of 3.0 mg. of estrogen and 90.0 mg. of progesterone) administered orally are effective hemostatics to functional uterine bleeding.

3. Crystalline progesterone administered orally is effectively metabolized by the human being as reflected in the progestational response of the endometrium which follows its daily administration over a period of ten days in a dose of 90.0 mg. daily.

4. Amenorrhea and oligomenorrhea resulting from pituitary-ovarian failure can be symptomatically relieved by the daily oral administration of the mixed natural estrogens, 3.0 mg., and crystalline progesterone, 90.0 mg. for ten days on the fifteenth through the twenty-fourth days of three consecutive cycles. Cyclic uterine bleeding can be induced in over half the patients while under such therapy and a smaller percentage will continue to menstruate regularly after discontinuing treatment.

5. Functional uterine bleeding offers the best clinical indication for the use of oral cyclic steroid therapy. The mixed natural estrogens in a dose of 3.0 mg. daily together with crystalline progesterone, 90.0 daily on the fifteenth through the twenty-fourth days of three consecutive cycles will establish rhythmic bleeding in the great majority of patients while under treatment. The relapse rate after three months of such therapy does not exceed 50 per cent.

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Medical Arts Building

ANTEPARTUM DICUMAROL THERAPY

RICHARD V. MANSELL, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology of the Methodist Hospital of Brooklyn, and the Department of Obstetrics and Gynecology, State University of New York at New York City, College of Medicine)

THE value of Dicumarol in venous thrombosis is well recognized,[1] yet in the antepartum period there are two cogent reasons for hesitancy: first, the danger of hemorrhagic complications to the mother; second, the possible deleterious effects on the growth and development of the fetus induced by the transmission of the anticoagulant effect across the placental barrier. Both experience in animals and case reports concerning human beings have rightly stressed the dangers of Dicumarol use.

For example, Schofield,[2] Roderick and Shalk[3] have shown that newborn calves born of cows which had been fed spoiled sweet clover hay exhibited hemorrhagic tendencies and were more sensitive to this agent than the mature animals. Quick[4] gave dogs in their last week of pregnancy therapeutic doses of Dicumarol. The newborn pups showed hemorrhagic tendencies and none survived unless vitamin K was given. He concluded that Dicumarol was contraindicated during pregnancy. Further studies[5] of the effects of therapeutic levels on pregnant rabbits showed that they did not have any excessive intrapartum and postpartum bleeding but that the newborns exhibited hemorrhagic tendencies. The longest survival time was five days and a few fetuses died before delivery. From this it was deduced that Dicumarol passed the placental barrier.

In human beings, von Syndow[6] observed one patient who received 1,750 mg. of the drug during the last month of pregnancy. The newborn showed cerebral and severe subcutaneous hemorrhages. Sachs and Labate[7] reported administering 3,750 mg. of Dicumarol to an antepartum patient in the last trimester. The fetus died in utero after 53 days of therapy. Examination revealed hemorrhages of the lungs, thorax, and pericardium.

In contrast, several authors have mentioned administering a course of anticoagulant therapy during the antepartum period without apparent deleterious effects on the mother or child. Yahr[8] mentions two patients treated in the third and seventh months, respectively, who received about 1,000 mg. of Dicumarol over 7 days. Both patients were subsequently delivered of normal children. Felder[9] had a similar experience in two cases in the first and third trimesters and Adamson[10] records three cases in the third, sixth, and eighth months and one at 8½ months. It is of note that these authors do not mention the total dosage administered. Davis[11] cited a case in which 800 mg. of Dicumarol had been administered during the twenty-eighth week of pregnancy. This patient, too, did well and delivered a normal child at term. Weiss,[12] Thornton,[13] and Ware[14] have added another six cases. In addition, ten cases have been treated safely with Tromexan[15, 16] and one with Heparin/Pitkin Menstruum.[17]

This study includes five antepartum patients who were treated with Dicumarol in their eleventh, twentieth, twenty-fourth, and thirty-second weeks

of pregnancy. Particular emphasis is given one patient who started treatment at the eighth week of gestation and received it almost continuously for thirty-one weeks, without detriment to mother or child.

CASE 1.—Mrs. A. K., 29 years old, white, American, gravida i, para 0, Rh negative, whose last menstrual period was April 10, 1950, was admitted to the Methodist Hospital June 15, 1950, in the eighth week of her pregnancy, complaining of pain and swelling of the right lower extremity of twelve hours' duration. Past history was irrelevant except for a dilatation and curettage and cervical biopsy in 1949; diagnosis, chronic cervicitis. Because the patient threatened to abort as evidenced by a brownish vaginal discharge from May 23 to 29, she was placed on a routine of bed rest at home, stilbestrol (Smith and Smith regime), vitamins, iron, and thyroid. On June 9 she was allowed out of bed and was subsequently well until the night before admission when she noted vague discomfort of the medial aspect of the right thigh. She was hospitalized the following day with a diagnosis of: (1) right femero-iliac thrombophlebitis, (2) 8 weeks' gestation. Admission examination revealed temperature 99.4° F., pulse 84, respirations 20. There was swelling of the entire right lower extremity, cyanosis on standing, and tenderness along the course of the femoral vein extending into the groin.

Laboratory Data on Admission.—Red blood cells 3.5 million, hemoglobin 10.8 Gm., white blood cells 9,900 with normal differential, sedimentation rate 3, coagulation time (Lee White) 7 minutes, and prothrombin time 14 seconds. The following day the white blood cells rose to 12,800 with polymorphonuclear leukocytes 82, lymphocytes 15, monocytes 2, eosinophiles 1. The therapy instituted was the same regime as at home and anticoagulants commenced. Depo-heparin was administered in 200 mg. doses for the first and second days and then discontinued. Dicumarol doses during this time were 300 mg. and 200 mg., respectively. Daily capillary coagulation and prothrombin times were performed, the former rising to 22 minutes on the second day and falling to 10 minutes on the third day (normal 4 to 6 minutes). Dicumarol dosage was determined following the daily report of the prothrombin time. The course was as follows: The temperature remained at 99° F. except on two occasions when it rose to 99.8° and 101.2° F. on June 16 and 19, respectively; the pulse varied between 74 and 100. The thrombophlebitis gradually subsided. During the 28 day course in the hospital, the prothrombin times ranged from 17 to 35 seconds (control 14 to 17 seconds). Daily Dicumarol dosage ranged from 50 to 300 mg. except for the fifth hospital day when none was administered because the prothrombin time rose to 35 seconds. Sedimentation rates varied between 67 and 86. The patient was discharged on July 12 (the twenty-eighth hospital day) and advised to continue Dicumarol, stilbestrol, thyroid, vitamins, iron, and wear an elastic stocking extending to the hip.

During the remainder of her antepartum course which was without mishap, prothrombin times were done at 1 to 2 week intervals, except from August 4 to 25 when the patient was on vacation but under care of a local physician. Weekly prothrombin determinations were done during the last six weeks of pregnancy. Stilbestrol was discontinued at the end of the thirty-fifth week, the total daily dose then being 125 mg. Throughout this time, Dicumarol was taken in 50 mg. doses daily, except in the following instances: from July 12 to 19 100 mg. daily; from November 1 to 3 100 mg. daily, following which 50 mg. and 100 mg. were alternated until November 10. On November 30, when the prothrombin time was 68 seconds, Dicumarol was discontinued until December 4, after which 50 mg. daily were continued until the thirty-seventh week, after which she took it six of each seven days. On January 4 and 5, 50 mg. tablets were taken. Prothrombin time was 22 seconds.

On Jan. 6, 1951, the membranes ruptured spontaneously and active labor began 12 hours later. The patient was given 72 mg. of vitamin K intravenously on admission and 1,000 c.c. of blood were made available. The patient was delivered 18 hours later, by prophylactic low forceps and a left mediolateral episiotomy, of a live male infant weighing

6 pounds, 1½ ounces. One ampule of Ergotrate was administered intravenously with the delivery of the anterior shoulder and a normal third stage of 5 minutes occurred. Blood loss was minimal.

The infant cried and breathed well immediately. The bleeding time taken in the delivery room was 3½ minutes. The child was normal in all respects. Subsequent laboratory data revealed a normal blood count and coagulation time, type O, Rh positive, and negative Coombs test. The time between the last dose of Dicumarol and birth was 36 hours.

The mother was up and about the morning after delivery. Dicumarol was started on the second postpartum day and continued throughout her stay in the hospital. Her postpartum course was uneventful. The patient was discharged on the tenth postpartum day when therapy was discontinued. Prothrombin times during the hospital stay ranged from 14 to 33 seconds (controls 11 to 16 seconds). Daily Dicumarol dosage varied between 50 and 200 mg. The pathological report of the placenta was: "Placenta, mature; infarct, small."

The total dosage of Dicumarol during the antepartum course was 12,100 mg. administered over 31 weeks.

CASE 2.—Mrs. A. D., a 31-year-old, white gravida ii, para i, Rh positive, whose last menstrual period was Dec. 20, 1946, was admitted to the Methodist Hospital March 7, 1947, with a diagnosis of (1) thrombophlebitis, left saphenous vein; (2) pulmonary infarction; (3) 11 weeks' gestation. She was placed on Dicumarol therapy for 8 of her 22 hospital days with doses ranging from 100 to 300 mg. Prothrombin times ranged from 14.4 to 97 seconds (controls 14.7 to 24 seconds). On the fifth hospital day, a left femoral vein ligation was performed. She was discharged March 28, 1947 (the twenty-second hospital day). The patient was readmitted one week later, April 5, because of a recurrent left leg thrombophlebitis and heparin was given in daily doses of 150 mg., 175 mg., and 100 mg., respectively. Dicumarol was also instituted on admission and she subsequently received 9 doses varying from 100 to 300 mg. Prothrombin times ranged from 16 to 60 seconds (controls 13.1 to 17.8 seconds). She was delivered Oct. 7, 1947 (estimated date of confinement September 27) of a normal 7 pound, 9 ounce male infant after a one-hour labor. Her postpartum course was normal. Circumcision performed on the sixth day was uneventful.

The total dosage of Dicumarol was 2,400 mg. administered over 43 days.

CASE 3.—Mrs. A. R., a 38-year-old gravida iii, para ii, Rh positive, whose last menstrual period was May 5, 1950, was admitted to the Methodist Hospital Sept. 26, 1950, with a diagnosis of: (1) acute superficial thrombophlebitis of the left calf; (2) 20 weeks' gestation. Past history revealed varicosities which had been present since her first pregnancy 14 years previously. She was treated with Depo-heparin, 300 mg. doses for the first two days. Dicumarol was administered for 26 of her 39 hospital days with doses ranging from 50 to 300 mg. Capillary coagulation time rose to 13 minutes. Prothrombin times varied between 15 and 43 seconds (controls 14 to 19 seconds). She was discharged on Nov. 3, 1950 (the thirty-ninth hospital day). On Feb. 7, 1951 (two days before her estimated date of confinement) she was delivered of a normal 7 pound, 10 ounce female after a three-hour labor. The postpartum course was uneventful.

The total dosage of Dicumarol was 2,500 mg. administered over 32 days.

CASE 4.—Mrs. G. A., a 26-year-old, white gravida ii, para i, Rh positive, whose last menstrual period was Oct. 28, 1947, was admitted to the Methodist Hospital April 14, 1948, with a diagnosis of: (1) thrombophlebitis, right leg; (2) 24 weeks' gestation. She was treated with Dicumarol for 12 of her 20 hospital days with doses ranging from 50 to 300 mg. Prothrombin times ranged from 15.2 to 39.1 seconds (controls 13.5 to 17.7 seconds). She was discharged May 3, 1948 (the twentieth hospital day). She did not receive any further Dicumarol during the rest of her antepartum course. On July 29, 1948 (six days before her estimated date of confinement) she was delivered of a live, normal male infant,

7 pounds, 7 ounces, after a two and one-half hour labor. The postpartum course was normal. On August 2, the coagulation time of the infant was normal. On August 3, a circumcision was performed without hemorrhage.

The total dosage of Dicumarol was 1,600 mg. administered over 15 days.

CASE 5.—Mrs. D. S., a 34-year-old, gravida iv, para iii, Rh positive, whose last menstrual period was Dec. 30, 1949, was admitted to the Methodist Hospital Aug. 15, 1950, with a diagnosis of: (1) Acute thrombophlebitis of the left leg; (2) 32 weeks' gestation. She was placed on Dicumarol therapy for 20 of her 22 hospital days. Doses ranged from 50 to 300 mg. Prothrombin times ranged from 14 to 39 seconds (controls 14 to 16 seconds). A 200 mg. dose of Depo-heparin was also administered on the day of admission. Following her discharge on September 5 (the twenty-second hospital day), daily doses were taken ranging from 50 to 75 mg. Weekly prothrombin times varied from 18 to 47 seconds (controls 15 to 16 seconds). On Oct. 5, 1950 (estimated date of confinement October 9) she was delivered of a normal 8 pound, 4 ounce female after a four-hour labor.

The total dosage of Dicumarol was 3,400 mg. administered over 42 days.

TABLE I

PATIENT	AGE (YEARS)	GRAVIDITY AND PARITY	DURATION OF PREGNANCY AT ONSET OF THROMBOSIS	DIAGNOSIS	DURATION OF THERAPY	TOTAL DICUMAROL DOSAGE IN MG.	TIME BETWEEN LAST DOSE AND DELIVERY
A. K.	29	G i, P 0	8 weeks	Femero-iliac thrombophlebitis (right)	31 weeks	12,100	36 hours
A. D.	31	G ii, P i	11 weeks	1. Pulmonary infarction 2. Saphenous thrombophlebitis (left)	43 days	2,400	24 weeks
A. R.	38	G iii, P ii	20 weeks	Acute superficial thrombophlebitis (left calf)	32 days	2,500	14 weeks
G. A.	26	G ii, P i	24 weeks	Thrombophlebitis (right leg)	15 days	1,600	13 weeks
D. S.	34	G iv, P iii	32 weeks	Acute thrombophlebitis (left leg)	42 days	3,400	10 days

Note.—No complications were noted and no maternal or fetal mortality occurred.

Comment

The use of Dicumarol in antepartum venous thrombosis will be justified only if the risks attending its use are significantly less than the risks of venous thrombosis untreated with anticoagulants. Venous thrombosis as a complication of antepartum period is comparatively rare. Most figures vary from about 0.037 per cent[18] to 0.1 per cent.[19] The prognosis in such cases therefore remains obscure because of insufficient data from which to form a definite conclusion. Most reports of thrombosis in obstetrical series cannot be used because no mention is made concerning the number of antepartum patients involved. A review of the literature to date reveals 80 cases of antepartum thrombosis untreated with anticoagulants in which there were 15 cases of pulmonary emboli with 12 fatalities (Table II). Twenty-nine cases were collected which were treated with anticoagulants and to this series we have added five cases. Five of these 34 treated cases had pulmonary emboli prior to therapy but there were no fatalities (Table III). While we cannot draw any signifi-

cant conclusion from these meager data, the fact that 80 cases of antepartum thrombosis untreated with anticoagulants had 12 fatal emboli (15 per cent) indicates the condition is a serious one and not to be treated lightly. Since Dicumarol has been shown to reduce fatal emboli, pulmonary infarction, morbidity, hospital days, and prevent the spread of the thrombus,[1] it would seem logical to afford the antepartum patient the benefits of treatment provided its risk to mother and child is not too great.

That the use of Dicumarol is not without danger has been evidenced by 32 deaths ascribed to its use in the past ten years and the fact that for the past five years it was the commonest cause of fatalities resulting from drugs administered orally.[29] The majority of these deaths, however, were caused

TABLE II. ANTEPARTUM THROMBOSIS UNTREATED WITH ANTICOAGULANTS

AUTHOR AND YEAR	NO. OF CASES RECORDED	CASES WITH PULMONARY INFARCTS	FATAL EMBOLI
Remy,[20] 1922	3	3	3
Holzmann,[21] 1924	10	1	1
Knauer,[22] 1927	4	4	4
Bansillon and Pigeaud,[23] 1931	1	0	0
Laffont and Schebat,[24] 1932	1	1	1
Friedlander,[25] 1936	1	0	0
Walsh and Barone,[26] 1947	3	1	1
Nyklicek,[27] 1948	1	1	0
Donaldson,[28] 1950	48*	3	2
Davis,[11] 1951	2	0	0
Hallum and Newham,[18] 1951	5	1	0
Thornton,[3] 1951	1	0	0
Total	80	15	12 (15%)

*Original report included one case of Holzmann's which in this report is in his series.

TABLE III. ANTEPARTUM THROMBOSIS TREATED WITH ANTICOAGULANTS

AUTHOR AND YEAR	NO. OF CASES REPORTED	CASES WITH PULMONARY INFARCTS	FATAL EMBOLI
Yahr, Reich, and Egger,[8] 1945	2	0	0
Greene and Loewe,[17] 1947	1*	0	0
von Syndow,[6] 1947	1	0	0
Felder,[9] 1949	2	0	0
Sachs and Labate,[7] 1949	1	1†	0
Weiss and Turner,[12] 1949	1	0	0
Adamson, Weaver, and Jaimet,[10] 1950	5	1	0
Davis,[11] 1951	1	0	0
Thornton,[13] 1951	2	0	0
Ware,[14] 1951	3	0	0
Wright, H.,[15] 1951	9‡	1	0
Wright, I.,[16] 1951	1‡	1	0
Mansell, 1951	5	1	0
Total	34	5	0

*Treated with Heparin/Pitkin Menstruum.
†Had three further episodes all when prothrombin times fell to normal.
‡Treated with Tromexan.

by gross overdosage. Duryee[30] states: "I believe we should not be alarmed by these serious complications but be guided rather by the successes as compared to the failures. When one looks back on the early days of the use of digitalis and sulfonamides he finds many deaths attributed to them. If one balances the deaths of Dicumarol against the individuals whose lives have been saved from anticoagulant therapy, I believe we have sound grounds for con-

tinued anticoagulant therapy. Until we evaluate the successes against the failures we will not be able to place these therapeutic agents in their proper places."

In regard to the effects of Dicumarol on the mother and her unborn child, several questions must be answered.

1. What levels were reached in respect to prothrombin times?
2. How consistently were they maintained?
3. At what stage of pregnancy was anticoagulant therapy used?

Brambel[31] recommends prothrombin times up to 25 to 30 seconds (40 to 50 per cent of normal) as sufficient prophylaxis against thromboembolism without greatly increasing the potentiality of hemorrhage. Cases 3, 4, and 5 were kept well within this range. Case 2 had several rises varying between 40 and 97 seconds and, in view of this, Dicumarol was discontinued. In regard to Case 1, since the patient had been treated as having a threatened abortion, it was decided to keep the prothrombin time on the low side (about 25 seconds) of the usually accepted therapeutic value. Sachs and Labate[7] have stated that prolonged Dicumarol therapy was dangerous to the fetus because prothrombin levels could not be used as an index of fetal response. They administered 3,750 mg. over a 53 day period. In this series, Case 1 received 12,100 mg. over 31 weeks; Case 2, 2,400 mg. over 43 days; Case, 3, 2,500 mg. over 32 days; Case 4, 1,600 mg. over 15 days; and Case 5, 3,400 mg. over 42 days. In none of these cases was the fetus affected, even in Case 1 receiving three times as much Dicumarol as reported by Sachs and Labate.[7] The fact that therapy was instituted during the most critical part of the life of the fetus, i.e., in the first trimester, in Cases 1 and 2, makes it all the more interesting that no deformities of the fetus occurred. Case 2 had prothrombin times between 14.4 and 97 seconds and yet no effect detrimental to the fetus was noted.

From the fact that none of these patients aborted, had any episodes of uterine bleeding or fetal abnormalities, it would appear that when safe levels of prothrombin time (25 to 30 seconds) are maintained when Dicumarol is given, we may have nothing to fear in these respects as long as vigilance is practiced. Constant observation of the patient is necessary and essential, and Dicumarol should be discontinued, as was done, if the prothrombin time becomes too great.

It is admitted that this series is small, but observation in these five cases would seem to indicate that Dicumarol may be employed in the antepartum patient without untoward effects to the mother or child provided the patient is under constant supervision and observation.

Summary

1. The literature on antepartum venous thrombosis has been reviewed and the seriousness of the condition evaluated.

2. The use of Dicumarol for antepartum thrombosis has been reviewed.

3. Five cases of antepartum venous thrombosis treated safely with Dicumarol have been added to the literature.

I wish to express my appreciation to the members of the staff for permission to utilize their cases in this report and to Dr. Anna Popescu for her assistance in translation of the foreign literature.

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130 Eighth Avenue

THE ROENTGENOGRAPHIC DIAGNOSIS OF ENDOMETRITIS HYPERPLASTICA OVARIALIS

SALVATORE DIPALMA, M.D., AND S. L. BERANBAUM, M.D., NEW YORK, N. Y.

(From the Departments of Obstetrics and Gynecology and Radiology, New York Post-Graduate Medical School, New York University-Bellevue Medical Center)

ENDOMETRITIS hyperplastica ovarialis is one of the varieties of metropathia hemorrhagica as the term is used by Schröder.[1] This condition is a definite endocrine entity characterized by uterine bleeding from a mucosa having the characteristics of an endometrial overgrowth due to the absence of normal ovulation and corpus luteum formation. It represents a type of "anovulatory menstruation," but the bleeding may not necessarily occur periodically and the endometrium has certain features which distinguish it from the normal preovulatory phase and from other types of functional bleeding.

Cullen[2] in 1900 published a description of the lesion and later established the close relationship to abnormal uterine bleeding naming it "hyperplasia of the endometrium."

Since then, a number of investigators considered and discussed the relationship of the ovaries with the endometrial findings. It remained, however, for R. Schröder, who thoroughly studied this condition from 1915 to 1919, to give us a complete analysis of the whole problem with a large series of cases, and he agreed with the theory advanced by Brennecke of persistent ripening follicles. Since then a number of contributions have appeared in the literature, the majority attributing the symptomatology of the abnormal uterine bleeding to ovarian changes characterized by abnormal persistent ripening follicles and corpus luteum formation.

Incidence.—This condition occurs between puberty and the menopause, and is the most frequent cause of the so-called functional bleeding. Fluhmann[14] found it in 54 per cent of 90 cases of this type of bleeding. He also reports it in 2.8 per cent of 1,750 hospital admissions to the Stanford Gynecological service.

Etiology.—The actual cause of this endocrine imbalance is, in our opinion, unknown. What is universally accepted at present is that the uterine pathology is due to prolonged ovarian hyperestrinism acting on a uterine mucosa without the normal controlling influence of progesterone. We concur with this theory and the clinical experience of one of us (diP.) leads us to believe that the hyperestrinism and absence of normal corpus luteum is due to a pathological condition of the maturing phase of the ovum, that is the process by which the ovum prepares for possible fertilization by losing half of its nuclear chromatin. It is well known that normally a woman will bring to maturity but a single ovarian follicle in each cycle. If many follicles should go toward maturation without one actually maturing in the sense just mentioned, we might expect an abnormally large production of estrin with an abnormally low production of

progesterone. The formation of a normal ovum or follicle depends on a normal secretion of both estrin and progesterone. The pathology thus occurs during the process of follicle maturation and the ovum would not mature sufficiently to be fertilized. The periodic abnormal multi-hyperfolliculation with its consequent excessive estrin action on the endometrium without a counterbalancing effect of progesterone might easily explain the endometrial pathology and the symptomatology. What actually causes this ovum's abnormal maturation is not as yet known although it would seem to depend on abnormal pituitary stimuli. In a number of cases operated upon by one of us (diP.) for excessive functional bleeding the ovaries were always found well developed and often enlarged. In the partially excised portion, microscopic examination always showed numerous follicles in varying stages of development and many scars similar to corpora albicantia but much smaller. A normal corpus luteum was not seen at operation nor on microscopic examination. In one case in which the bleeding had existed for over two years, during which time a physician was not consulted, the patient when first seen had a hemoglobin of 40 per cent and a large hard uterus the size of a six weeks' pregnancy. A diagnosis of a fibromyoma of the uterus was made and, after transfusion, a high supracervical hysterectomy was done. It was noted at the time that the ovaries were large but of normal appearance. On cutting the specimen, it was found that the uterine cavity was completely filled by a spongy mass about 4 cm. at its widest diameter—the microscopic diagnosis was "hypertrophic endometritis, Swiss cheese type." Another almost identical case was personally reported to us by Dr. Gerard Moench. These two cases demonstrate the effect of a very prolonged hyperestrinism on the uterine mucosa to the extent of producing large polypoid and fungoid growths which, on coalescing, formed one mass enclosed by the body of the uterus, thus simulating a fibroid uterus.

Pathology.—The pathological changes in the uterine mucosa vary, depending on the degree of hyperestrinism, the duration of its action, and on whether treatment has been given.

The ovaries noted in one case were healthy looking, normal in appearance, and the outstanding gross characteristic was the marked increase in size. In the case of a young Negro girl they were so large that a preoperative diagnosis of chronic "pus tubes" was made. Microscopically, they present the typical picture in which Graafian follicles are present in large numbers, in various stages of development, a few almost developing to maturation. The majority of them, however, appear as false granulosa theca lutein cysts or as small false corpora albicantia.

We believe that Schröder's concept that hyperestrinism is due to a pathological persistence of ripening follicles, that Meyer's opinion as to hyperfolliculation, and that our own concept that it is due to an incomplete ovum maturation are all tenable from the microscopic appearance of the ovaries.

Endometrium.—The gross endometrial changes are always characterized by marked thickening, with a surface showing irregular prominences which might be described as having a fungoid or polypoid appearance or a combinatioin of

both. Microscopically, the appearance varies in the bleeding or nonbleeding phase, also as to the length of its duration, and as to whether treatment has been given. In the nonbleeding cases the mucosa has practically the same features throughout its thickness—the stroma is dense and cellular, the cells show active growth, are spindle shaped, and there are many mitotic figures. The glands have a haphazard arrangement. Their number is markedly increased, and great variation in the size of their lumina is evident. The cells lining the glands are also variable, some showing only one layer of cylindrical epithelium; in none is a true secretory phase seen. Other glands may show irregularity in size, and cystlike sacs lined by low cuboidal epithelium, giving the typical "Swiss cheese" pattern. Still other glands may be lined with stratified layers of epithelium showing marked growth and the presence of mitotic figures. In bleeding cases, besides the changes just described, we may see areas of necrosis due either to mechanical interference of the blood supply or to heavy infiltration of polys simulating a traumatic inflammation.

Symptoms—Age Incidence.—According to Novak and Martzloff,[15] Fluhmann, and Schröder, the majority of cases occur between the ages of 25 years and the menopause. The condition affects both nulliparous and multiparous women. In Fluhmann's series eight had from one to five spontaneous abortions. Those women failed to carry their pregnancies to the viable stage and this strengthens the hypothesis that the defect is due to an abnormal maturation of the ovum. In cases where there is prolonged bleeding, a secondary anemia, varying in severity, is always associated. Characteristic of this bleeding is the fact that it is a prolonged, painless metrorrhagia and that it quite often follows a period of amenorrhea. Bimanual pelvic examination shows no evident pathology except that the ovaries may be enlarged and often are tender. When this entity exists in married women there is usually a history of sterility, again strengthening the opinion that the etiology is an abnormal, incomplete ovulation.

Diagnosis.—The diagnosis of this type of endometritis is made by the history and the microscopic appearance of the endometrium. Hormonal tests are impractical and inconclusive.

Prognosis.—This is usually poor in very long-standing cases because pathological changes have occurred in the ovaries and uterus which are irreversible without multilating operations. When the condition is treated early, particularly in the younger subject, the prognosis is good—as a matter of fact, some do get well without any treatment.

Treatment is divided into: first, endocrine; second, radiation; third, surgical. The endocrine treatment consists in the administration of chorionic gonadotropic hormone and progesterone. Good results have been reported. Our experience with these hormones has been disappointing. However, the administration of thyroid and testosterone in fairly large doses has been found satisfactory in some of the bleeding cases. It must be admitted that this type of therapy exerts a depressant action on the ovulatory phase of the ovary and in some instances the condition has returned in from six months to a year following treatment.

The surgical treatment consists in the removal of a section of ovary and seems to have given good results. The exact explanation of why this follows is not clear. Surgical procedures were done only after repeated failures of endocrine and radiation treatment.

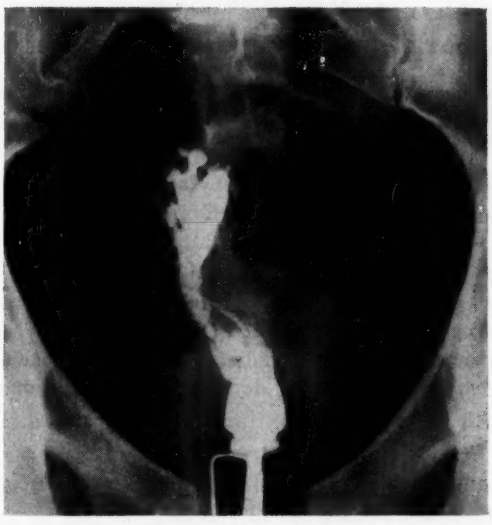

Fig. 1.—Exposure taken during salpingography with the fractional method on M. M. on Jan. 3, 1950, showing marked distortion of the uterine cavity with multiple small irregular excavations throughout the entire area resulting in a Swiss cheese type of pattern which is characteristic of this condition.

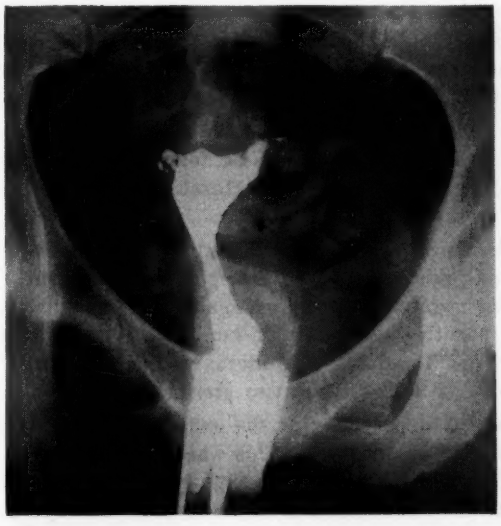

Fig. 2.—Follow-up salpingography on Nov. 10, 1950, after treatment with radium. The irregular crisscross Swiss cheese type of pattern is no longer evident. There still remains a slight irregularity near both cornua with still no filling of the Fallopian tubes.

Radiation treatment consists of small doses of x-ray over both ovaries (80 r to the depth of each ovary), or small doses of intrauterine radiation (400 to 600 mg. or mc. hr.) which have seemed to benefit a certain number of patients.

Naturally, when this condition occurs near or at the menopause, a sterilizing dose of radium or x-ray stops the bleeding permanently by producing an immediate menopause.

The importance of the roentgenographic diagnosis of this entity has to our knowledge not been stressed in the literature. Neither has there appeared a description of the roentgen findings. The following case report is therefore included to illustrate the diagnostic and therapeutic procedures employed.

M. M., a 26-year-old housewife, was referred for gynecological examination and opinion on account of sterility of two years' duration. Examination of the husband's semen was normal.

She had been originally seen in April, 1943, by another physician and she gave a history of continuous menses of four months' duration. Examination at that time showed a moderately overweight woman of 19 years of age, normal in every other respect, and showing no objective signs of any endocrine disturbance, except for obesity.

In May, 1943, under general anesthesia, a pelvic examination and diagnostic curettage were performed. The uterus was normal in size, anterior, and freely movable. The curettage showed a considerable amount of polypoid endometrium. The conclusion at that time was that she was suffering from uterine bleeding due possibly to ovarian dysfunction.

She was treated with Antuitrin S for three months, and a normal menstrual cycle followed.

She was seen by another physician in 1948, complaining of irregular menses.

On May 20, 1949, she again complained of irregular menses to still another doctor. He found the uterus somewhat larger than normal, with a mass in the cul-de-sac about the size of a tangerine. She was treated at this time with thyroid extract and estinyl which established a normal menstrual rhythm.

On Jan. 6, 1950, she was seen by a surgeon who recommended an exploratory laparotomy for the cystic mass previously described. This was performed on Jan. 17, 1950, at which time a pedunculated clear cystic tumor about the size of a small grapefruit was found arising from the left ovary. The mass was removed. The uterus itself contained a small intramural fibroid in the left side of the fundus, which was enucleated. A prophylactic appendectomy was performed.

Her menstruation since the operation was as follows: on January 25, it continued for nine days; on March 1, seven days; and on March 28, twelve days. She and her husband were then referred as a problem in infertility.

Examination at this time showed a normal adult white woman, slightly obese, weight 152 pounds, with low blood pressure (90/60), hemoglobin 80 per cent, minus 12 basal metabolism rate, and an otherwise negative physical examination. The external genitals and internal pelvic examination were negative. In view of her history a hysterosalpingogram was performed on May 1, 1950 (Figs. 1 and 2). The uterus was enlarged with an irregular crisscross defect resembling Swiss cheese filling the entire uterine cavity.

A tentative diagnosis of hyperplasia of the endometrium of the Swiss cheese type was made and diagnostic curettage was advised. This was done on June 27, 1950. The following note was made at operation: "The uterus was slightly enlarged, the cavity measuring 8 cm. in length. The endometrium was thick and copious, soft and spongy." The pathological diagnosis was hyperplasia of the endometrium of the Swiss cheese type.

It is our belief that a possible cause of the sterility was the marked hyperplasia, particularly at the ostia of the tubes. This might well cause a blockage, preventing the entrance of the spermatozoa into the tubes, and preventing an ovum from entering the uterine cavity.

She was advised to have another salpingogram a few weeks after her diagnostic curettage, but she failed to appear until Sept. 6, 1950, at which time the uterine pathological condition had recurred.

At that time it was suggested that another curettage be performed with the administration of 800 mc. hr. of radium emanation. This was done on Sept. 23, 1950. She reported for another salpingogram on Nov. 10, 1950, approximately two months later. At this time the marked Swiss cheese type of appearance was not present throughout the body of the uterus. Hyperplastic changes were still observed at the ostia of the tubes.

Conclusions

1. The endocrine entity commonly called hyperplasia of the endometrium should be called "endometritis hyperplastica ovarialis."

2. The condition is characterized by abnormal ovum maturation, and by hyperestrinism due to multiple folliculation and an abnormal corpus luteum formation.

3. The diagnosis of the condition should not be made without a curettage which shows the typical microscopic findings.

4. The prognosis is usually good with endocrine or radiation treatment.

5. Characteristic roentgen pictures are presented.

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1103 Park Avenue

THE PRESUMABLY WELL WOMAN

A. C. Siddall, M.D., F.A.C.S., Oberlin, Ohio

IT IS a striking fact that individual preventive medicine has been applied in private practice by only two groups of physicians: pediatricians and obstetricians. Since obstetrics and gynecology are usually combined as a specialty, it is surprising that the preventive methods used in the care of the antepartum patient during the past fifty years have not been proffered to that same woman after her infant has been born. Many gynecologists still confine their major interest only to those patients with pathological findings and for this reason any effort to extend more routine attention toward the woman with no serious complaints should be timely.

This communication reports the results of a venture into individual preventive medicine in gynecologic practice. It is an attempt to aid those women who are apparently well to stay well.

During the past eight years I have encouraged the presumably well woman to come to my office for a semiannual examination. A total of 2,264 examinations have been made on 1,131 examinees and the findings as given below indicate that the asymptomatic woman does present a problem that deserves more attention from the gynecologist than has been given in the past. From the beginning of this study the chief emphasis has been on the early detection of pelvic cancer and this aspect of the problem was first presented in 1949.[1] Now after two additional years the early detection of cancer continues to hold the major interest but repeated discovery of many unexpected benign lesions, habit problems, and minor psychiatric disturbances has broadened this project both in interest and importance. This report confirms a previous impression that the presumably well woman who is not pregnant welcomes a routine inventory of her general health just as she does when pregnant. She is prepared to pay for cancer detection in private practice and seeks advice as to habits, rest, diet, recreation, and marital relations.

The methods followed in these studies of the well woman continue to be simple and inexpensive. By the term "presumably well" is meant the woman with no or minor complaints and without signs and symptoms suggestive of cancer. The suggested routine is a history and complete physical examination followed in six months by a breast-pelvis examination only. The laboratory tests include a hemoglobin determination, urinalysis, and a cytological spread from the uterine cervix. Biopsies are taken of all suspicious lesions. X-ray examinations and other laboratory tests are ordered as indicated. In order to avoid the criticism of pressure tactics, reminder cards are not sent to these women to stimulate return visits unless they request them. Education concerning cancer is carried out during the routine interview and by means of leaflets furnished by the American Cancer Society. Since no special publicity has been given to this pro-

gram new examinees appear each year usually because some friend has told them of her own previous experience. The average number of new examinees each year for the past eight years under study was 141. The return visits for a complete examination far outnumbered the return visits for the pelvis-breast examination as indicated in Table I. Only 145 examinees made four or more visits during the eight years under investigation. Six examinees came for 8 visits; 13 for 7 visits; 25 examinees for 6 visits; 32 for 5 visits; and 69 for 4 visits. This leaves the large majority of 986 examinees who came for only one to three examinations throughout the eight-year period. Approximately one hour of each day in the office has been required to carry out this program.

If the suggested plan of a semiannual examination had been followed by each of the 1,131 women in this report, the total number of examinations would have been 11,562.

TABLE I. FIRST AND RETURN VISITS

COMPLETE EXAMINATION		PELVIS-BREAST EXAMINATION	TOTAL	TOTAL
FIRST VISITS	RETURN VISITS	RETURN VISITS	RETURN VISITS	EXAMINATIONS
1,131	953	180	1,133	2,264

The age distribution remains about the same through the eight years under study with over half of all examinees below 40 years of age. It would be desirable to have more women in the older age group since the incidence of cancer is highest there. However, it must be remembered that cancer is the leading cause of death not only for women 40 to 59 years of age but also for those from 30 to 44 years.[2] The age groups are given in Table II.

TABLE II. AGE DISTRIBUTION

	AGE IN YEARS				
FIRST VISITS	UNDER 30	30-39	40-49	50-59	60 AND OVER
1,131	411	254	208	146	112

Six hundred twenty-five women examined were married and had borne children, while 270 were married but nulliparous and only 186 were unmarried and nulliparous. Eighty-one per cent of the cancers found in these examinees were in the married women who had borne children and who were forty years of age or older.

Experience reported here with the cytological smear or spread (Papanicolaou[3]) from the uterine cervix, indicates that it is of great value in searching for early carcinoma of the cervix. To date 580 cytological spreads have been taken; 563 from the well women in the Detection Group and 27 spreads from the patients in the Diagnostic Group or those women with signs suggestive of cancer at the time of the first visit. In Table III are summarized the results of the cervical cytological spread in proved cases of uterine carcinoma.

The significant factor about the cytological spread is that in every proved case of carcinoma of the cervix the spread showed malignant cells, and no false positives were reported. On the other hand, in no case were malignant cells reported in spreads taken from the four patients with endometrial carcinoma, but in one case atypical cells were found and the spread laboratory advised a curettage for diagnosis. However, the cytological spreads that were taken following the curettage in each case showed many malignant cells. All

of these adenocarcinomas of the endometrium were small, early lesions and apparently did not exfoliate their cells. Reagan[4] has pointed out that identification of adenocarcinoma is less satisfactory by the cytological technique.

TABLE III. CYTOLOGICAL SPREAD FROM PROVED CASES OF UTERINE CANCER

EXAMINEE	MALIGNANT CELLS	FINAL DIAGNOSIS
Detection Group.—		
L. D.	positive	Carcinoma in situ, cervix
R. S.	positive	Carcinoma in situ, cervix
Diagnostic Group.—		
M. R.	positive	Carcinoma in situ, cervix
D. S.	positive	Squamous-cell ca., cervix
M. H.	positive	Squamous-cell ca., cervix
D. F.	negative	Adenocarcinoma, endometrium
C. W.	negative	Adenocarcinoma, endometrium
A. C.	negative	Adenocarcinoma, endometrium
C. L.	negative	Adenocarcinoma, endometrium

In searching for cancer in asymptomatic women the complete physical examination is necessary for otherwise the reassurance that can be given the patient is far from satisfactory. If these 2,264 examinations on 1,131 presumably well women had been confined to the pelvis alone then only 3 cancers would have been found over the eight years under analysis, namely, two in the cervix uteri and one in the fundus of the uterus. However, when these examinations included the breasts of these same women, 4 additional cancers came to light. Finally, when these same examinees were submitted to a complete physical examination, 9 more cancers were added, bringing the total number of cancers to 16. The number of cancers found in the relation to the extent of the examination is presented in Table IV.

TABLE IV. DETECTION GROUP.* CANCERS FOUND IN RELATION TO EXTENT OF EXAMINATION

PELVIS		PELVIS-BREAST		COMPLETE	
		Cervix uteri	2	Cervix uteri	2
Cervix uteri	2	Fundus uteri	1	Fundus uteri	1
Fundus uteri	1	Breast	4	Breast	4
				Bowel	4
				Lymph nodes (Hodgkin's disease)	1
				Blood (leukemia)	1
				Skin	3
Total	3		7		16

*Presumably well women.

Nine of the cancers found in the Detection Group were in an early stage and a favorable prognosis could be given following treatment: carcinoma in situ of cervix uteri 2, breast 3, bowel 1, and skin 3. If the case with Hodgkin's disease and the case of leukemia are dropped out of consideration because they are not amenable to treatment, 5 cases are left in which delay on the part of the patient led to late detection and unfavorable prognosis.

Both cases of carcinoma in situ of the cervix uteri were first brought to light by means of the cytological spread.

CASE 1.—A 43-year-old married woman, gravida ii, para 0, came for a routine physical examination. She had no complaints except a slight amount of nonirritating leukorrhea during the previous year. Her menstrual periods were regular, once in thirty days, with a flow of five days' duration. No intermenstrual spotting had been noted. Pelvic examination revealed a fundus uteri average in size, movable, with one small, firm, round nodule felt on the right side. No adnexal masses were present and the cervix was smooth

and clean. The cytological spread was positive for malignant cells and the diagnosis of carcinoma in situ of the cervix was confirmed by the histopathological examination of the uterine curettings. At the time of the operation the fundus was found to be small and smooth except for a small myoma on the right side and after total removal of the uterus no gross evidence of the carcinoma could be seen. The left tube and ovary were removed and the patient made an uneventful recovery.

CASE 2.—This was a 38-year-old married woman gravida iv, para iii, whose history and physical examination were essentially negative in 1948. However, when she reported for examination two years later she complained of spotting of blood occasionally between her regular menstrual periods during the previous six months. The last episode of spotting occurred following coitus one week before her visit to the office. The pelvic examination revealed the cervix to be somewhat thickened with a healed lateral laceration. No erosion was present. The fundus was anterior, of average size, and no pelvic masses were palpable. The cytological spread showed malignant cells of the squamous type to be present. The rule to confirm the spread report by tissue diagnosis before treatment was deliberately violated in this case but the histopathological confirmation of carcinoma in situ was made following total hysterectomy and bilateral salpingo-oophorectomy.

Those patients who come to the office with signs and symptoms suggestive of cancer at the time of the first visit are not included in the Detection Group but are in another series called the Diagnostic Group. During the eight years under study 22 cancers have been found in this Diagnostic Group, as follows: cervix uteri 10, corpus uteri 3, ovary 2, vulva 1, breast 3, bowel 1, skin 2. Only 6 of these 22 cancers were found in an early stage with a favorable prognosis following treatment, namely, carcinoma in situ of cervix uteri 1, adenocarcinoma of the endometrium 3, and skin 2. The carcinoma in situ in this group was found in the cervical stump eighteen years following subtotal hysterectomy. This patient was a 58-year-old woman, para i, who reported at the time of her first visit that she had noticed on two occasions a few spots of bloody mucus from the vagina during the previous three months. Pelvic examination revealed no induration and no masses in the pelvis. The cervix was of average size, movable, smooth except for a small granular erosion on the posterior lip. The cytological spread revealed malignant cells typical for carcinoma in situ and this was confirmed by examination of the curettings. The cervix was excised and the pathologist reported that no carcinoma was evident in the specimen.

All of the cancers that were discovered outside the pelvis were referred to the general surgeon for treatment. These patients subsequently returned to my office for their semiannual examinations.

One case of interest in this category of nonpelvic cancer was that of a 61-year-old married woman, para ii, who had had a total hysterectomy ten years previously. Her only complaint was a mild constipation and mild recurrent crampy pains in the left lower quadrant of the abdomen, during the previous six months. Her bowel movements were twice daily but the amount of each movement was smaller than usual. No blood was ever noticed in the stools, the appetite was normal and there had been no loss of weight. The physical examination revealed nothing abnormal but with this history a barium enema was ordered and the roentgenologist reported a constricting lesion in the sigmoid colon. A segment of the colon containing a well-differentiated adenocarcinoma was resected and the patient is well and free from metastasis after seven years.

The benign lesions that come to light in examining well women are of real importance in the realm of cancer prevention and early treatment is desirable. The vast majority of the 346 benign lesions in this series were found by pelvic examination but when a complete examination was done 55 lesions were dis-

covered in the breast and 25 in the thyroid gland. These benign lesions are listed in Table V, and show the lesions found in relation to the extent of the examination made.

Some of these benign lesions develop to a large size without the examinee being aware of their presence and two cases are reported to illustrate this fact.

TABLE V. DETECTION GROUP. BENIGN LESIONS IN RELATION TO EXTENT OF EXAMINATION

TYPE OF EXAMINATION					
PELVIS		BREAST-PELVIS		COMPLETE	
Cervical erosions (cervicitis)	116	Pelvic lesions	266	Pelvic lesions	266
Cervical polyp	34	Cystic mastitis	49	Breast lesions	55
Cervical fibroma	1	Fibroma	1	Thyroid adenoma	25
Uterine polyp	1	Lipoma	1		
Uterine myoma	54	Adenoma	4		
Endometriosis	14				
Ovary, cystic tumors	21				
Salpingitis, tuberculous	1				
Vaginitis	6				
Gartner's duct cyst	6				
Paraurethral cyst	1				
Urethral caruncle	5				
Bartholin gland cyst	1				
Hidradenoma	1				
Vulvitis	3				
Condyloma acuminatum	1				
Total	266		321		346

CASE 1.—A nulliparous, unmarried woman, 43 years of age, came to my office for routine physical examination. She had no special complaints. The menstrual periods were regular, once in 28 days with a flow 3 to 5 days in duration and moderate in amount with no cramps. She complained of no leukorrhea. The pelvic examination revealed a large smooth, firm, freely movable mass which filled the pelvis and extended upward to the umbilicus. It was attached to the fundus of a small uterus. No other masses were felt. A cytological spread from the cervix uteri showed no malignant cells. The diagnosis of uterine myoma was confirmed at the time of operation, it being subserous and attached to the dome of the fundus. The right tube was adherent to a cystic right ovary so these were removed along with the subtotal hysterectomy. Many dense adhesions between the sigmoid and the cervix prevented a total removal of the uterus. The recovery was uneventful.

CASE 2.—A 29-year-old woman, para i, came to the office for a routine physical examination. She reported that her menstrual periods were fairly regular once in 28 days, moderate amount of flow for four or five days and accompanied by no pain. There had been some feeling of fullness in the left lower quadrant of the abdomen for approximately two months. The pelvic examination revealed a cystic mass which filled the pelvis and pushed the average-sized fundus toward the right side. This cyst at the time of operation proved to be a pseudomucinous cystadenoma of the left ovary and it measured 16 cm. in diameter. It was easily removed and the patient made an uneventful recovery. Thirteen months later this patient became pregnant and at full term successfully completed her second pregnancy. One year and seven months before this cyst was found this patient had been examined and no evidence of a cyst was present at that time.

The routine history that is taken during this study includes questions regarding diet, rest, recreation, exercise, and habits of drinking, smoking, and sexual practices. Therefore, at the conclusion of every examination specific instruction is given regarding these points.

The question of worry and anxiety is raised with each examinee after the examination is completed when the woman is more at ease and has sensed a

friendly, sympathetic attitude toward her problems. Usually without hesitation various anxieties are admitted and the fear of cancer is one of the most frequent. However, without exception these women are relieved of much of their cancerphobia and they are willing to carry out self-examination of the breast as directed.

Two questions arise at this point: First, whether this attitude and practice of becoming interested in the general welfare of the presumably well woman falls within the field of gynecology? Second, should these well women be sent first to the general practitioner or the internist who in turn calls in the gynecologist only when pelvic pathology is found or suspected? If the future development of gynecology is to become strictly a surgical specialty then the answer is yes to the second question above. If the concept continues that gynecology is both medical and surgical in scope then the future development of this specialty should follow an expanding program of preventive medicine along the avenues already trod so successfully by the obstetrician. The woman who fears cancer fears it just as much whether it be found in the uterus or the breast or the bowel, and for this reason a complete examination should be offered to these women. Certainly the gynecologist who confines his examination to the pelvis and then refers the examinee to the internist is doing his whole duty but in a subrural private practice such as is here reported it is more satisfactory and economical to the patient to carry out the complete examination and follow this with what treatment or referral for treatment is indicated.

Summary

1. A venture in preventive medicine in private gynecologic practice is reported covering a period of eight years during which time 2,264 examinations were done on 1,131 presumably well women.

2. The primary emphasis in this study was on the early detection of pelvic cancer and of a total of 16 cancers found, only 3 were in the pelvis, namely, cervix uteri 2, fundus uteri 1.

3. During the eight years under study 22 more cancers have been found in women who presented signs suggestive of a malignant condition at the time of the first visit. Of the 22 cancers in this Diagnostic Group 16 were in the pelvis, namely, cervix uteri 10, fundus uteri 3, ovary 2, vulva 1.

4. A total of 356 benign lesions were revealed and appropriate treatment given.

5. Problems of diet, rest, recreation, marital relations, and minor psychiatric disturbances were considered and treated.

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47 College Place

A RECENT ADVANCE IN ESTROGENIC THERAPY. II.

WALTER J. REICH, M.D., MITCHELL J. NECHTOW, M.D., ALVIN M. KURZON, M.D., AND M. WM. RUBENSTEIN, M.D., CHICAGO, ILL.

(From the Departments of Gynecology of the Cook County Hospital, Grant Hospital, and Chicago Medical School)

IN a previous publication, the clinical effectiveness of piperazine estrone sulfate (Sulestrex-Abbott) in the control of menopausal symptoms was demonstrated.[1] On the basis of subjective relief and vaginal bioassays on twenty-five patients, it was concluded that this preparation promoted quick clinical response with an unusual minimum of untoward side effects.

An additional 175 patients have now received this therapy and the response has been evaluated. One hundred patients were treated with this estrogenic substance for menopausal symptoms. Fifty were observed for the ability of the medication to inhibit postpartum lactation, and twenty-five patients were treated for menopausal symptoms with a combination of piperazine estrone sulfate and methyltestosterone.

Treatment of the Menopause

Using our previous method of classification (mild, moderately severe, and severe), the menopausal patients were evaluated on the basis of their subjective complaints (Table I).

TABLE I. CLASSIFICATION AND TREATMENT GROUPING

	NO PREVIOUS TREATMENT			PREVIOUS TREATMENT				
CLASSIFICATION	MILD	MODERATELY SEVERE	SEVERE	MILD	MODERATELY SEVERE	SEVERE	TOTAL	
Artificial	5			4			9	Mild
		9			7		16	Mod Sv
			10			5	15	Severe
Natural	21			14			35	Mild
		11			9		20	Mod Sv
			3			2	5	Severe
	26	20	13	18	16	7	100	

Mild.—There were forty-four patients thus classified. These patients received initial doses of Sulestrex varying from 0.75 to 1.75 mg. Complete relief of symptoms was obtained in thirty-eight patients, and satisfactory control in an additional five. One patient did not benefit by therapy.

Second courses of therapy were instituted on the five patients receiving partial but satisfactory relief on the basis that our original classification, perhaps, minimized the character of the symptoms and our initial dosage was accordingly inadequate. By increasing the dosage to 4.5 mg. per day, all patients were brought under control with complete subjective palliation.

In the mild group, then, the percentage of satisfactory clinical response was 95.4.

Moderately Severe.—Thirty-six patients came into this category and received dosages varying from 1.5 mg. per day and upward. Thirty-three patients

were given complete relief from all symptoms. One patient still complained of occasional headaches, but expressed satisfaction with the treatment. Two patients did not respond to any variation in therapy. These were surgical castrates.

The percentage of adequate clinical response in this group was 91.6 per cent.

Severe.—As in our previous series, this group exhibited the most difficult problems in therapy. Of the twenty patients placed in this classification, the clinical response in thirteen patients was graded satisfactory. The dosage varied from 3.0 to 6.75 mg. per day. Despite cyclic therapy, treatment had to be discontinued in two patients, because of very profuse withdrawal bleeding. Unsatisfactory results in the remaining five patients labeled them as failures.

The percentage of ample clinical control in this group was, then, 65 per cent.

In an effort to improve our results and simultaneously compare the single estrogenic substance with a combination of estrogen and testosterone, the five patients who did not respond to the usual method of treatment were recalled for treatment with the combined preparation. These results are recorded later.

The combined results of therapy with piperazine estrone sulfate (PES) are as follows (Table II):

TABLE II. RESULTS OF THERAPY

GROUPS	NO. OF PATIENTS	SATISFACTORY	NOT SATISFACTORY	PERCENTAGE
Mild	44	43	1	95.4
Moderately Severe	36	33	3	91.6
Severe	20	13	7	65.0
Total	100	89	11	89.0

Excellent results can be expected in the groups with mild and moderately severe symptoms. As Table II reveals, seventy-six of eighty patients showed satisfactory results (95 per cent). Fairly good results can be expected in the group with severe symptoms; approximately two of three patients will benefit with this therapy. We feel that much better results should not be anticipated since well over half of the women in this group are usually surgical castrates who repeatedly demonstrate resistance to therapy, and the other half demonstrate menopausal symptoms tainted with additional somatic complaints. It might be well to speculate on the psychogenic factors that could be involved with these patients. Nevertheless, in any group of appreciable size, approximately nine of ten patients will be given adequate subjective relief.

Inhibition of Postpartum Lactation

The property of estrogenic substances to inhibit lactation in the parturient woman is well known. With fairly large doses the formation of the pituitary lactotrophic hormone is probably suppressed, thus relieving the non-nursing patient of burdensome engorgement and unnecessary milk production. While we do not subscribe to the overzealous use of this type of therapy, we feel that, where indicated, its utilization is acceptable.

Diethylstilbestrol has been most widely used for this purpose. Its potency is well standardized, and its low cost provides economy. However, troublesome untoward reactions, sometimes delayed, make it a much less desirable medicament than claimed. Frequently there is a rebound mammary engorgement oc-

curring about the fourteenth day post partum which is often most distressing to the patient and difficult to explain away by the attending doctor. Even more worrisome is the appearance of fairly profuse vaginal bleeding about a week after the drug has been discontinued. And not too infrequently, the medication fails to accomplish its mission, especially if started after lactation has been established. These are disqualifying characteristics and leave much to be desired. With this in mind, PES was given to fifty postpartum patients and its effects studied.

This group was divided in half; twenty-five patients were started on the medication within twenty-four hours of delivery, and twenty-five placed under treatment after lactation had manifested itself. The dosage administered was calculated on the basis of the comparative potencies of diethylstilbestrol and estrone sulfate. Stilbestrol is about five times as potent by weight as estrone sulfate. However, about 50 per cent of its effect is lost when given orally, hence it is about three times stronger than its equivalent weight of estrone sulfate. Since the average daily dose of diethylstilbestrol for suppression of lactation is 15 mg. daily, or 8 mg. of activity, the equal dose of piperazine estrone sulfate would be about 18 to 24 mg.

Tablets containing 3 mg. of PES were utilized. The course of treatment consisted of a daily intake of 18 to 24 mg. for three days, followed by 12 mg. daily for the next two days, irrespective of what time therapy was instituted. Our results are recorded in Table III. These figures indicate that PES can be expected to relieve completely nine out of ten patients of lactation engorgement if treatment is started within twenty-four hours of delivery, and that this percentage rapidly diminishes as the interval between delivery and therapy grows. Once the mammae have filled, less than one-half can be afforded relief with the medication alone.

TABLE III. RESULTS OF THERAPY WITH REFERENCE TO TIME TREATMENT STARTED

	PRELACTATION		POSTLACTATION	
Failure	0		10	(40%)
Complete relief	24	(92%)	10	(40%)
Partial relief	1	(8%)	5	(20%)
	25		25	

All patients were followed for an additional six weeks post hospitalization. One patient experienced "rebound" engorgement necessitating analgesics for pain and dehydration for relief. One patient had minimal bleeding beginning sixteen days after delivery, six days after the lochia had disappeared.

Estrogen-Testosterone Therapy

As indicated earlier, six patients who did not respond to therapy with PES were recalled for treatment and placed on a combination of PES with methyltestosterone. An additional nineteen patients were similarly studied.

Detailed symptomatic classification of the cases was not attempted except to differentiate the severe types from the mild forms.

The medication was available in the form of soluble lingual tablets and in combinations of (1) PES, 0.75 mg., with testosterone 5 mg., and (2) PES, 1.5 mg. with testosterone 10 mg.

The six previously treated patients (group with severe symptoms) placed on this second therapeutic regime received dosages varying from two tablets of combination No. 1 to four tablets of combination No. 2 per day. Only one pa-

tient in this group experienced any relief in her symptoms. This would infer that if a given subject is to be afforded subjective relief of her symptoms, it is not influenced by the type or combination of medication, but instead by dosage.

The remaining nineteen cases were of the mild and moderately severe type. On a similar dosage scale, as described above, seventeen (89.5 per cent) had responded favorably. This figure approximates the percentage results obtained with the unit medication (PES) and would indicate no significant difference based on the type of drug used. Whether or not a certain symptom complex would favor the use of one or the other is not apparent to us in this study.

Comment

There is no doubt that the large majority of women with climacteric symptoms can be given gratifying relief with hormonal therapy. Whether or not these symptoms are directly proportional to a degree or level of ovarian insufficiency or due to some other factor is not argued. An appreciation of this possibility, however, is a mandate in appraising the value of any form of medicinal therapy. This factor becomes apparent when the results of treatment are graded, in so far as they are related to the severity of the case type.

The surgical castrate and the patient with ill-related psychosomatic complaints, other than those accepted as characteristic of the climacterium, have been and will be resistant to hormonal therapy in a large percentage of cases. This should not be accepted as being due to failure of the particular medication, but rather due to the incompatibility of diagnosis and treatment. The list of symptoms ascribed to the menopause are not peculiar to that entity. Hence, confusion in diagnosis will err on the side of treatment, giving false values to recorded studies.

Summary

1. A pilot study has revealed a clinical effectiveness of piperazine estrone sulfate in reference to subjective relief and response of the vaginal epithelium. The preparation is extremely well tolerated, regardless of dosage. The annoying urinary taste and odor, sometimes found in natural conjugated estrogen, is not present. There is an unusual minimum of side reactions.

2. An additional 125 patients with menopausal symptoms have been similarly treated and the results evaluated. Satisfactory response can be expected in nine out of ten patients with mild to moderately severe complaints. Approximately two of three patients with severe symptoms can be given relief. The lack of response in at least one-third of this group is probably due to other etiological factors (presumably psychogenic) and does not reflect any inadequacy of the treatment using hormones. There seems to be no difference in the results obtained whether an estrogen alone or in combination with testosterone is utilized.

3. Fifty parturient women were placed on Sulestrex to study its ability to inhibit lactation. The successful outcome appears dependent on the time therapy is initiated. If treatment is started within twenty-four hours after delivery, a satisfactory result can be anticipated. Nine of ten patients thus treated with piperazine estrone sulfate obtained optimum results. Therapy with the same drug was successful in less than 50 per cent of the patients, if started after lactation had been established. Rebound engorgement and withdrawal bleeding occurred only twice in the thirty-four cases successfully managed.

4. Treatment for the menopausal symptoms with the combination of estrogen and testosterone does not appear to have any significant advantage over estrogen alone.

Conclusion

Piperazine estrone sulfate (Sulestrex-Abbott) is a clinically effective oral estrogenic substance, easy to administer and extremely well tolerated. Its action is accompanied with an amazingly low incidence of side reactions. An appreciation of the psychosomatic component which simulates the menopausal complex is necessary when evaluating results obtained.

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109 North Wabash Avenue

DANGERS OF IMPROPER VAGINAL DOUCHING

DONALD V. HIRST, M.D., COUNCIL BLUFFS, IOWA

(From the Department of Obstetrics and Gynecology, Jennie Edmundson Memorial Hospital)

FOR several years the author has made a careful inquiry into the vaginal douching habits of obstetric and gynecologic patients seen in the office. The results of this inquiry are markedly interesting and worth reporting for two facts which it brings out. First, it is not generally appreciated that improper methods of routine vaginal douching are morbific and dangerous. Second, there is a great deal of unawareness on the part of patients and physicians alike in regard to the reasons or indications for vaginal douching, and particularly the criteria of a proper physiologic douche.

In considering the first point a review of the literature uncovered only one article[1] reporting a proved case of a serious outcome of an apparently routine vaginal douche. In this case Natenshon reports on a nonpregnant, parous Negro woman of 30 years of age who collapsed from severe abdominal pain following the introduction of a small amount of douche solution. An emergency laparotomy revealed a fairly large amount of thick yellowish fluid in the peritoneal cavity with no gross pathology of the pelvic organs or evidence of trauma. The patient made an uneventful recovery. Inquiry revealed that the patient had douched with a hot solution of vinegar and baking soda. It was thought that the gas generated by this solution might have forced foreign material or solution into the peritoneal cavity through the cervix, uterus, and tubes.

Other examples of accidents occurring through an intact cervix are found in the reports of maternal deaths following the vaginal insufflation of medicinal powders during pregnancy.[2] These parallel cases have one causal factor in common: air or fluid under pressure in the vagina. That this set of conditions is particularly dangerous in the pregnant woman is well understood, but that it can also be dangerous in the nonpregnant woman is not so well understood. Karnaky[3] reports that in fluoroscopic observations on six menstruating women he was not able to pass sodium iodide solution higher than the internal cervical os with pressures up to 200 mm. of mercury. He does not state, however, whether these women were parous or nulliparous, nor did he state the condition of their cervices. It cannot be assumed, therefore, that it is difficult or impossible to pass solutions retrograde through the cervical canal in all women, or even only at excessive pressures. A lacerated and patulous cervical os is such a commonly observed sequela of childbearing, one would suppose that in such women it would be comparatively easy to force fluid from the vagina through the cervical canal into the uterus and tubes by the use of pressure.

That this in fact does happen is indicated by the following case histories, and the thesis is presented herewith that a significant portion of the acute and chronic cases of salpingitis and pelvic inflammatory disease which occur in women without obvious etiology or frank venereal disease are caused by retrograde passage of vaginal douche fluid under pressure with contamination and infection of the female pelvic organs.

CASE 1.—(No. 12-45124) This 33-year-old white housewife, para ii-0-ii, was seen in the office with a presenting complaint of a brownish vaginal discharge which had occurred for several days before and after menstruation for the previous three months. She had

been referred by her family physician who had been treating her without success. Her last two episodes of bleeding were acyclic but not excessive. For the few days prior to her first visit she had noted moderate low pelvic pain not referred to either side. Questioning revealed that she douched with a hand-bulb type of apparatus with an occlusive vaginal cuff for inflation of the vagina with douche fluid under pressure.

Pelvic examination by speculum revealed a brownish discharge from the cervical os with no defects of the cervical or vaginal mucosa. Bimanual palpation showed the uterus slightly enlarged and heavier than normal, and tender to pressure and movement. The left adnexal region was very tender with thickening but no mass. The right adnexal region was not remarkable.

A diagnosis of subacute left salpingitis and probable endometritis was made. The patient was given daily parenteral penicillin at the office and told to take long, hot douches at home after being instructed in the proper douching techniques and apparatus.

At an office visit two weeks later she had no complaints and had had no menstruation. Pelvic examination showed no discharge and only uterine tenderness. She was instructed in the proper technique of douching with vinegar and asked to keep a record of her periods.

Six weeks after her first visit she reported two menstrual periods at approximately 21 day intervals with slight premenstrual spotting but no discharge. She stated she felt well and had no complaints. Pelvic examination showed the cervix and uterus normal with slight tenderness and thickening in the left adnexal region.

CASE 2.—(No. 21526) This 27-year-old white housewife, para i-0-i, came into the office complaining of amenorrhea of 3 months' duration, a small amount of daily bleeding for the past two weeks, and mild abdominal cramps for the past 2 days. She stated that she had been taking pressure douches for the past several years one to three times a week. Her past history showed that she had been treated for sterility 4 years previously at which time she was found to have a low basal metabolic rate for which she had received thyroid. Three years ago she had a normal pregnancy and delivery. She and her husband had been trying for pregnancy for several months.

Examination revealed suprapubic tenderness to deep palpation without masses. Speculum showed a copious foul pinkish discharge coming from the cervical os. The uterus was in mid-position, firm, slightly enlarged, and very tender to movement and pressure. Both adnexal regions were very tender to palpation but without masses or thickening. A diagnosis of acute pelvic inflammatory disease was made. Pregnancy was suspected but could not be proved clinically. The patient was given daily parenteral penicillin and instructed to take long hot douches.

Three days later she brought in the products of conception which she had passed spontaneously and completely. A formal gross pathological report stated: "Specimen consists of portions of decidual tissue together with an amniotic sac containing a fetus which measures 1.5 cm. in length." The microscopic report stated: "Placental and decidual tissue show severe acute inflammation and necrosis. The severity of the inflammation is out of proportion to the amount of necrosis and might indicate infection introduced through the cervix." The diagnosis was amended to include an infected complete abortion.

Ten days later the patient was seen in the office without complaints and apparently feeling quite well. Examination showed the cervix and vagina clean and well covered. There was a slight bloody discharge from the cervical os but it did not appear purulent. The uterus was anterior, normal in size, freely movable without pain. The adnexal regions were not tender and no masses or thickening were palpable.

CASE 3.—(No. 9215128) This 30-year-old white housewife, para 0-0-0, came to the office complaining of recurrent episodes of pelvic pain. She had had such an episode in the past week. Eight years previously she had had a right tubal infection with severe pain which responded well to antibiotics. Inquiry revealed that she had always douched with pressure using a hand-bulb type of syringe with an occlusive introital cuff.

Pelvic examination showed the mucosal surfaces of the vagina and cervix to be normal in appearance and intact. There was a brownish mucoid discharge from the cervical os.

Bimanual palpation showed the uterus anterior, normal in size, but drawn to the right of the midline and somewhat fixed and tender to movement. The right adnexal region was thickened and tender without a definite palpable mass. The left adnexal region was not remarkable. A diagnosis of subacute and chronic pelvic inflammatory disease due to pressure douching was made.

The patient was instructed in the proper apparatus and techniques for taking vinegar and long hot douches alternately, and was returned home without specific medication.

Six weeks later she reported feeling quite well and without pelvic pain. Examination showed the uterus displaced to the right as before with some tenderness on movement which was referred to the right adnexal region. There was still some thickening in the right adnexal region but no direct tenderness and the rest of the examination was not remarkable.

CASE 4.—(No. 8135126) This 32-year-old housewife, para ii-0-ii, was first seen in the office with the complaint of severe lower abdominal pain of 24 hours' duration followed by soreness without nausea or vomiting, fever, constipation, diarrhea, or urinary symptoms. She stated that she had had similar episodes during the previous 2 to 3 years about every three months, but that in the previous 5 to 6 months she had had seizures every month. She gave a history of routine pressure douching. Her past history was not remarkable and she recounted a normal menstrual history without pelvic infections.

Examination revealed marked tenderness in both lower quadrants of the abdomen with slight tenderness at both costovertebral angles, but no masses or rigidity. Pelvic examination was normal throughout except for a minor laceration of the cervix without inflammation. There was no detectable tenderness or involvement of the adnexal regions.

In the absence of pelvic findings the possibility of tubal or peritoneal irritation by douche fluid was discarded, but the patient was warned and instructed in proper douche apparatus and techniques.

Hospitalization with expert consultation, laboratory studies, and x-ray studies of the gastrointestinal and genitourinary tracts showed no disease or apparent cause for her abdominal pain. This cleared spontaneously, however, and further talks with the patient revealed emotional problems which were thoroughly discussed with an improvement in her outlook.

Almost 16 weeks after her original visit she was seen in the office complaining of severe lower abdominal pain and cramps for the preceding few days following a menstrual period. Inquiry revealed that the patient was still using a hand-bulb pressure-douche syringe in spite of previous warnings and that she had taken a douche following her period. Examination showed marked lower abdominal tenderness bilaterally. Speculum showed the cervix and vagina clean and well covered without discharge from the cervical os. Bimanual palpation showed the uterus anterior and normal in size but very tender to movement and pressure. Both adnexal regions were extremely tender but there were no masses or thickening. A diagnosis of acute pelvic inflammatory disease from pressure douching was made and the patient was placed on parenteral penicillin therapy. Her pain and complaints subsided promptly and an examination a month later showed no remarkable findings in the pelvis.

CASE 5.—(No. 915113) This 31-year-old housewife came to the office complaining of a barren marriage of 6 years' duration. She denied the use of contraceptives. The husband was of proved fertility as he had two children by a previous marriage. He was 38 years old and in good general health. The patient claimed she had always been in good health and gave a normal menstrual history. Three years before she had developed a sudden acute pelvic infection which she was told involved the tubes. She was treated with parenteral penicillin and oral sulfonamides with good results. Since then, however, she had noted occasional pelvic pain and soreness, and moderate dyspareunia. The patient gave a history of routine pressure douching.

A general physical examination was not remarkable. Pelvic examination showed normal external genitals, and by speculum the vagina and cervix were clean and well covered.

Bimanual palpation showed the uterus posterior, not flexed, normal in size, but fixed and tender to movement. There were no findings in the adnexal regions. Rectal examination showed the uterosacral ligaments to be tense and tender.

A diagnosis of presumed sterility was made and the patient was given the important facts conducive to conception and was impressed with the need for a complete sterility survey. Proper douching apparatus and techniques were explained to her. Dates were arranged for an endometrial biopsy and a Rubin test. She did not keep her appointments.

Four and one-half months later she appeared in the office complaining of severe nausea of a week's duration and amenorrhea for the previous 7 weeks. Pelvic findings were indicative of an early pregnancy (which was proved later) and there was no pain or tenderness on examination. She stated that her pelvic soreness and dyspareunia had cleared up following the change to proper douching habits, and she attributed her pregnancy to the assistance from this change.

Comment

Whiston and Ellis[4] in an excellent review have thoroughly covered the whole subject of vaginal douches. Their article and the writings of Karnaky[3] epitomize the present-day attitude and informed opinion on this subject. Even these authorities disagree on some phases. Karnaky, for example, recommends acid douches after coitus as a hygienic measure, but Whiston and Ellis state that such douches are usually unnecessary. This latter view would seem more logical provided that both parties cleanse themselves with soap and water beforehand.

The whole question of the rationale of routine vaginal douches is inseparable from the fixed ideas the majority of women have in regard to their personal hygiene. From a strictly medical point of view there is little if any indication for routine douching in the absence of demonstrable pathology. The routine use, however, of vaginal douches for hygienic purposes is so universal the medical profession from a practical point of view is forced to recognize that a douche properly prepared and administered is harmless, that it is, therefore, an allowable concession to femininity, and, finally, that it is the responsibility of the medical profession to disseminate the correct information on this subject.

The following outline gives the accepted techniques and practices in the use of vaginal douches and is a compilation of the sources quoted and the opinions expressed above:

1. In order to avoid retrograde contamination and infection, douches should never be taken under pressure.

2. Two types of douches are recognized: the first, a warm douche solution for cleansing or hygiene, and the second, a prolonged hot douche using only hot tap water to provide heat to the pelvic organs.

3. A douche solution should always be acid—never alkaline—in order to maintain or promote the physiologic acidity of the vagina. The solution should have a pH below 5.0 and a convenient recommendation is ¼ to ⅓ of a cup of white vinegar or 2 teaspoonfuls of U.S.P. lactic acid to a 2 quart douche receptacle. If a douche powder is desirable only those powders giving a solution of the desired acid pH should be recommended.

4. Precoital alkaline douches to promote conception are ineffective and contraindicated.

5. The use of alkaline douches in the treatment of mycotic vaginitis is no more effective than acid douches and is contraphysiologic.

6. Acid vaginal jellies are more effective than douches for lowering and maintaining vaginal acid pH at the proper levels.

7. A douche should always be taken lying down with the knees drawn up and hips raised either on a bedpan or on a heavy folded towel in the bath tub.

The hips should be raised high enough so that the falling away of the intestinal viscera will provide negative pressure to aid in the distention of the vagina by the weight of the douche solution.

8. When a long hot douche is used, the temperature of the water is more important than the amount. An ordinary 2 quart douche bag filled with very hot water and with the flow carefully controlled by the pinch clamp on the tubing will provide a long hot douche of proper temperature and duration.[5]

9. Douches are not effective as a contraceptive measure.

10. Douches are not necessary for postcoital hygiene provided both parties cleanse themselves with soap and water beforehand.

11. There is no harm in douching during the menstrual flow.

12. Douche equipment should be cleansed with soap and water after use, and frequently sterilized by boiling.

Summary

Five cases are presented to show that vaginal douching with pressure is potentially dangerous and moribific. The thesis is presented that pressure douching is responsible for a significant portion of the acute and chronic cases of pelvic inflammatory disease. The use of routine vaginal douches is discussed and an outline is given indicating the proper practices and techniques.

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532 First Avenue

PELVIC PNEUMOPERITONEUM. THE X-RAY APPEARANCE OF THE NORMAL FEMALE PELVIC ORGANS

J. GERSHON-COHEN, M.D., AND M. B. HERMEL, M.D., PHILADELPHIA, PA.

(From the Albert Einstein Medical Center)

THE term "pelvic pneumoperitoneum" might be used to designate the procedure of inducing pneumoperitoneum to demonstrate the pelvic organs in x-ray films.[1, 2, 3, 5] The pneumoperitoneum can be induced either by the transabdominal or the transuterine route, using the Rubin test technique. In this way, this procedure could be differentiated from hysterosalpingography by which the interior of the uterus and tubes is outlined with an opaque substance to render them visible in x-ray films. The term "gynecography," as suggested by Stein,[7] could then be retained to designate his double contrast procedure of "hysterosalpingography" and "pelvic pneumoperitoneum."

Since we had available for study a group of 30 women, each of whom had a therapeutic pneumoperitoneum for pulmonary tuberculosis at Eagleville Sanatorium, this report is concerned with the x-ray technique and the appearance of the *normal* female pelvic viscera. None of these women had any signs or symptoms of pelvic disorder or disease.

Technique

The patient, to be properly prepared for this examination, should have the bladder and rectum emptied. A pneumoperitoneum with 500 to 1,000 c.c. of carbon dioxide is established either by the transabdominal or by the transuterine route.[1] The patient is then placed face down on the x-ray table with her thighs elevated over two pillows. An air pillow or balloon under the epigastrium serves to compress the air into the pelvis. This modified knee-chest position makes it possible to angle the x-ray beam axially through the pelvic canal (Fig. 1). An excellent outline of the uterus, tubes, ovaries, round ligaments, bladder, rectum, and other pelvic contents is obtained when the x-ray beam is angled 20 degrees cephalad (Fig. 2). Slightly oblique views occasionally are necessary to project the ovaries away from the pelvic brim. The x-ray technical factors which we use are 80 kv., 300 Ma., 40 inches distance, and a 16 to 1 ratio grid in the Potter-Bucky diaphragm.

Results

The axial view of the uterus obtained by pelvic pneumoperitoneum reveals a transverse ovoid shadow varying from 5 to 7 cm. in width and from 3 to 5 cm. in thickness. The lateral extensions formed by the tubes and round ligaments are clearly seen. The lower portion of the uterus may be denser than the upper due to the overlapping of the curving upper and lower uterine segments or to overlapping of the bladder. The relative positions of the uterus, bladder, and rectum are discerned easily, so that the presence of any extraneous masses between them can be detected. The surfaces of these three viscera are smooth. The ovaries are clearly seen as small ovoid masses in the lateral aspects of the pelvis measuring from 2 to 4 cm. in length and 1.5 to

3.0 cm. in width. The tubes vary in length and direction, averaging 3 to 6 mm. in thickness. They can be differentiated easily from the round ligaments which curve anteriorly toward the brim of the pelvis. These vary in thickness within the same range as the tubes. The bladder and rectum can be seen even when they are empty (Figs. 3 to 6).

Comment

The appearance of the normal female pelvic viscera is remarkably uniform within the limits noted above. The normal uterus, tubes, and ovaries always are well demonstrated if the technique has been correct. Congenital defects such as malposition or hypoplasia of the tubes, ovaries, and uterus could be recognized quickly. Other congenital irregularities such as bicornuate or duplex uterus could be suspected by a cleft, more or less complete, in the fundus; but to determine the presence of a septate or subseptate uterus, Stein's procedure of gynecography would have to be employed. Subserous

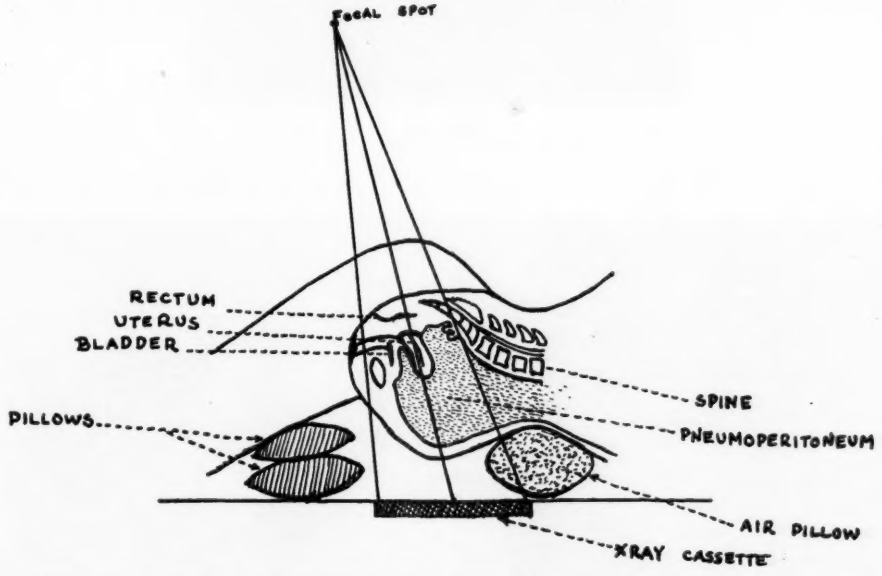

Fig. 1.—Position of patient and direction of x-ray beam for demonstrating pelvic organs with pneumoperitoneum.

or corporeal tumors should be seen by the change in contour from the normal silhouette caused by these lesions, but mucosal and submucosal infiltrations and tumors could be demonstrated only by the double contrast method of Stein and Arens.[6] When the diagnosis of pelvic lesions does not yield to clinical methods, then pelvic pneumoperitoneum might be of value. Small tumors in the body of the uterus, or in the tubes, ovaries, ligaments, or other pelvic structures can be demonstrated easily by pelvic pneumoperitoneum when not suspected by physical examination.[4] Stein demonstrated tubal pregnancy with ease by this method.[8]

The indications and contraindications for the use of gynecography[7] are also applicable to pelvic pneumoperitoneum. Indications for transabdominal pelvic pneumoperitoneum would include the differential diagnosis and complications of pregnancy during the first trimester, such as tubal pregnancy, associated cysts and fibroids, and visualization of the pelvic viscera for corroborative and/or differential diagnoses. Conversely, this method would not

be satisfactory in cases of ruptured tubal pregnancy, shock, poor surgical risks, or in elderly women, or for pathologic lesions too large to be visualized. Transuterine pelvic pneumoperitoneum would be of benefit in visualizing the pelvic status in sterility; it would demonstrate obscure pelvic lesions, especially those associated with sterility; and could be used as an optional

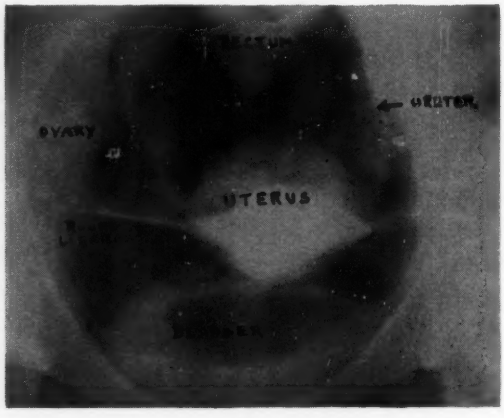

Fig. 2.

Fig. 3.

Fig. 4.

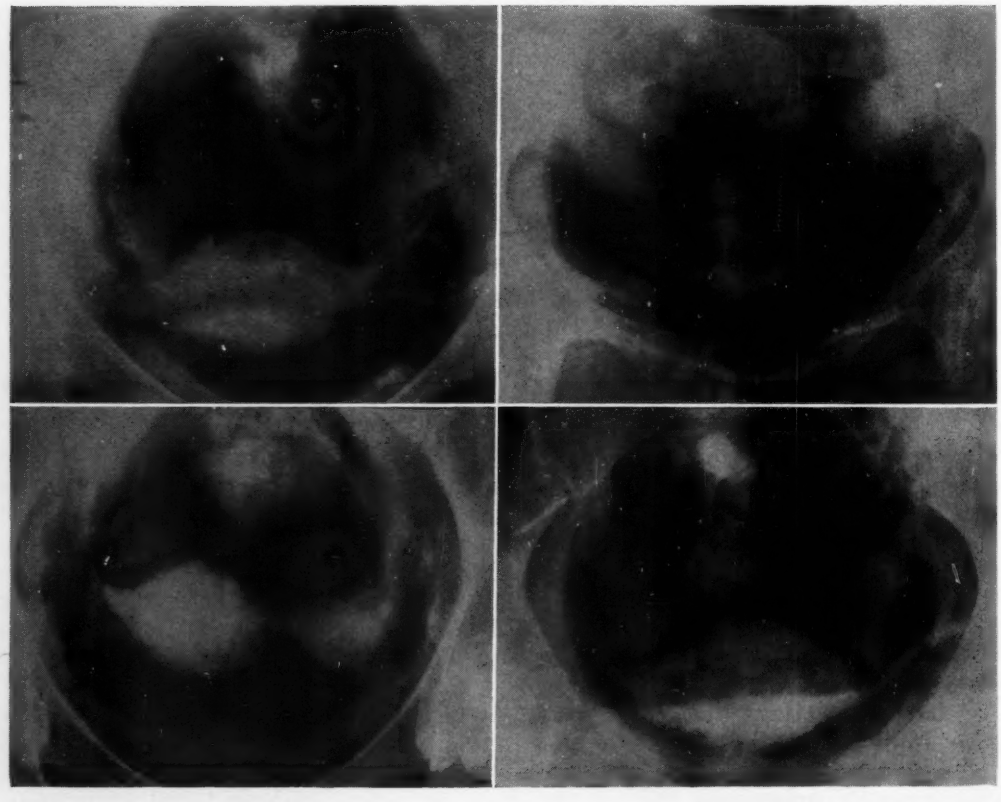

Fig. 5.

Fig. 6.

Figs. 2-6.—The x-ray appearance of the normal female pelvic organs with pneumoperitoneum.

method for pelvic diagnosis in women with patent tubes. However, contraindications would include pregnancy, normal or abnormal, vaginal bleeding, acute cervicitis, and pelvic inflammatory disease.

Summary

Pelvic pneumoperitoneum was used to study the appearance of normal pelvic organs in a group of 300 women with pulmonary tuberculosis, who had pneumoperitoneum for therapy. This method of demonstrating the pelvic contents offers many preoperative diagnostic possibilities, especially since the pneumoperitoneum can be established easily by the same technique as used in the Rubin test. The normal variations in the size, shape, position, and density of all the empty pelvic organs have been analyzed in this group; and these normal standards can be useful in the detection of minimal abnormal changes which otherwise might be difficult to recognize.

We gratefully acknowledge the kind cooperation of Dr. Robert V. Cohen, who selected cases for study from among his patients at Eagleville Sanatorium and Dispensary.

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255 South 17th Street

LOBECTOMY FOR PULMONARY TUBERCULOSIS DURING PREGNANCY

GEORGE SCHAEFER, M.D., AND HARRY H. EPSTEIN, M.D., FOREST HILLS, N. Y.

(From the Departments of Obstetrics and Gynecology and of Medicine, Triboro Hospital)

THE advent of streptomycin and pulmonary resection in the treatment of pulmonary tuberculosis has greatly decreased the morbidity and mortality in this disease. In many instances, streptomycin has stopped the spread of the tuberculous process and brought it under control so that surgical procedures to arrest the disease could be done. Segmental resection, lobectomy, and pneumonectomy have now enabled us to remove foci of tuberculosis that could not be controlled by pneumothorax, pneumonolysis, or thoracoplasty.

Active tuberculous disease does not remain stationary; it either progresses or regresses. Clinical experience has taught us that the earlier treatment can be instituted the better are the end results. Chamberlain[1] has stated that timing is as important to the successful surgical result as it is in a military operation and "that neither streptomycin nor any other drug can be expected to replace sound judgment in selecting the right operation for a specific patient, to be done at the proper time under good anesthesia and by a competent surgeon." We believe that the newer medical and surgical procedures for the treatment of pulmonary tuberculosis that have proved useful in the nonpregnant woman should not be withheld from the pregnant patient. We are further convinced, on the basis of a recent study,[2] that the performance of a therapeutic abortion in the tuberculous patient, thus delaying the necessary surgical procedure until the recovery from this operation, has not enhanced our results.

It was some time after its introduction that thoracoplasty was attempted on the tuberculous woman during pregnancy. At first a number of patients who became pregnant following thoracoplasty were carefully followed during gestation, labor, and in the puerperium. When it was observed that pregnancy had no deleterious effect on their tuberculous condition, thoracoplasties were attempted during pregnancy. A number of such cases with excellent results have been reported.[3, 4, 5] However, pulmonary resection is now replacing thoracoplasty in many institutions as the surgical procedure of choice for the treatment of pulmonary tuberculosis and the problem has arisen whether these procedures should be performed during pregnancy.

A review of the literature reveals only one case of pneumonectomy performed during pregnancy. In 1949 Thompson and Bressler[6] reported on a woman operated upon during the sixth month of gestation. The patient was a 29-year-old Puerto Rican admitted with caseous pneumonic tuberculosis during her pregnancy. Artificial pneumothorax failed to influence the cavities and six weeks after pneumothorax was started a pneumonectomy was performed. Two and one-half months after pneumonectomy the patient had a

premature vaginal delivery, assisted by outlet forceps, of a 5 pound, 1 ounce infant. Her postpartum course was uneventful and fourteen months after operation both mother and child were in excellent condition.

Material

We have delivered six patients following lobectomy or pulmonary resection performed before the onset of pregnancy. The course of pregnancy, the delivery and the puerperium in all patients were normal. We are now reporting a case in which a lobectomy was performed during the first trimester of pregnancy.

CASE HISTORY NO. 3248.—L. R., a 24-year-old white married woman, was admitted to Triboro Hospital for the second time on June 17, 1950. Pulmonary tuberculosis was first discovered in a routine chest x-ray in 1941 and she was admitted to Raybrook in 1942 where she was found to have a cavity in the apex of the right lung. Following eighteen months of bed rest, the cavity closed spontaneously and she was discharged in September, 1943, as having an arrested case. In December, 1943, the cavity was again seen in the right apex and she was readmitted to Raybrook where a right pneumothorax was instituted in January, 1944. In July, 1945, tomographic studies showed a lesion in the left upper lung.

She was admitted to Triboro for the first time on Nov. 10, 1945, where x-rays revealed bilateral pulmonary tuberculosis. In June, 1946, pneumothorax was started in the left side and successful pneumonolysis was done on the left side in September, 1946. In February, 1947, the pneumothorax on the right side was inadvertently lost and attempts at reinduction were unsuccessful. Sputa and gastric analysis were negative for acid-fast bacilli since May, 1946. Right upper lobotomographs and right lateral tomographs failed to demonstrate any cavity disease and the patient was discharged as having an arrested case with pneumothorax refills to be continued on the left side in the Outpatient Department.

On June 17, 1950, the patient had a pulmonary hemorrhage and was admitted to Triboro for the second time. X-rays demonstrated recurrence of the lesion on the right side. Sputum was positive for acid-fast bacilli. The opinion of the surgical conference was that the patient should have bilateral resectional surgery. On July 9, 1950, she was started on 1 Gm. of streptomycin every other day plus 10 Gm. of para-amino-salicylic acid every day until operation. In December, 1950, the pneumothorax space on the left side was lost.

On Jan. 11, 1951, a right upper lobectomy was performed under cyclopropane intratracheal anesthesia. The duration of the operative procedure was three and three-quarters hours and the patient received 2,000 c.c. of whole blood on the operating table. The pathological report was, "A right upper lobe having an irregular appearance, measuring 15 by 5 by 5 cm. The pleura is thick and ragged. Section reveals in one-half the specimen numerous encapsulated caseous foci lying in fibrotic parenchyma. The second half of the specimen shows caseous foci with a considerable aerated parenchyma, the foci varying from 3 mm. to 8 mm. in size. On microscopic examination the caseous foci show some central liquefaction. The delimitation of the caseous areas is possible. There are extensive fibrosis and bronchiectasis and areas of tuberculous bronchitis. The pathological diagnosis was: 1. Cavitation represented by caseous foci with liquefaction. 2. Tuberculous bronchitis. 3. Pulmonary fibrosis and bronchiectasis."

Immediately following operation streptomycin, 1 Gm. every 2 days, was given plus 10 Gm. PAS until Jan. 28, 1951, when streptomycin, 1 Gm. twice a day every 3 days was given.

The patient's last menstrual period was Dec. 11, 1950. She went home on a 48 hour pass on Dec. 24, 1950. Following operation she did not have a menstrual period in January, but this was thought to be due to the effect of the operative procedure. At the end of January she complained of slight morning nausea. Repeated urine tests for pregnancy were reported as toxic, probably due to the antibiotics she was receiving. Obstetrical consultation was requested on March 2, 1951, and revealed an intrauterine pregnancy of about eight weeks' duration in a primigravid woman.

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Dec. 15, 1950. Before lobectomy. There is an infiltration above and below the right clavicle with honeycombing. There is also an infiltration in the second left interspace with a small pneumothorax pocket overlying the left upper lobe.

Figs. 2 and 3.—Dec. 15, 1950. Tomographic studies demonstrate the honeycombed lesion in the right upper lobe as well as a circumscribed density with fibrosis in the left upper lobe.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—July 25, 1951. Six months after lobectomy, in the seventh month of gestation. Shows resection of fifth right posterior rib. The right middle and right lower lobes are fully expanded and no infiltrations can be made out. The left lung is fully expanded with dense fibrosis in the upper lobe.

Fig. 5.—Nov. 27, 1951. Eleven months after lobectomy, two months after delivery. There is no change from July 25, 1951.

Fig. 6.—Jan. 22, 1952. Twelve months after lobectomy, four months after delivery. There is no change in x-ray findings from previous films in July and November, 1951.

The question arose as to what to do about the pregnancy. Consultation with the medical, surgical, and obstetrical services decided to permit the pregnancy to proceed to term, continue the patient on streptomycin, and follow her carefully during her prenatal course. Sputa and gastric analysis remained negative throughout her antenatal course. Repeated chest x-rays revealed fibrotic disease on the left side with no definite areas of cavitation in the left upper lobe. Streptomycin, 1 Gm. twice a day every 3 days and PAS, 12 Gm. every day, were continued up to time of delivery. Regression of the disease on the left side took place and surgical intervention for this lesion was withheld. Her antenatal course was entirely normal with a weight gain of 23 pounds. She had no shortness of breath, felt well following operation, and was in an excellent frame of mind. She was pleased with the fact that the pregnancy was continuing to term.

On Sept. 30, 1951, the patient was delivered of a normal male infant weighing 6 pounds, 12 ounces. She received 100 mg. Demerol for analgesia plus cutaneous abdominal infiltration of Novocain. Delivery was effected under caudal anesthesia by low forceps and episiotomy after a 4½ hour labor. Her postpartum condition remained good. Sputa and gastric analyses continued negative and x-rays revealed no evidence of cavity on the left side. She was continued on streptomycin, 1 Gm. twice a day every 3 days. She left the hospital on Dec. 15, 1951, and returned to the Outpatient Department for a check-up on Jan. 29, 1952. She had been well since leaving the hospital and examination showed her condition to be unchanged. Both she and her infant were progressing normally.

X-ray of her course before, during, and after pregnancy are shown in Figs. 1-6.

Comment

We believe that any procedure to cure tuberculosis that would be done were the patient not pregnant should be performed during her pregnancy. If the patient first comes under observation after the seventh month of gestation, we would not advise a radical lung operation, but rather would suggest a course of streptomycin and PAS until delivery and afterward in preparation for surgery. Although we have not seen spontaneous abortion following thoracoplasties during the first seven months of pregnancy, we know that premature labor may follow any extensive surgical procedure in the last two months of pregnancy in the nontuberculous as well as in the tuberculous woman.

Our patient had a right upper lobectomy performed during the first trimester of her pregnancy. At the time of operation she had chronic bilateral pulmonary tuberculosis which had existed on the right side for ten years and on the left side for five years. Bed rest, pneumothorax, and pneumonolysis were unsuccessful in controlling her disease and it was felt that pulmonary resection offered her the only chance of cure. The pregnancy was not discovered until after operation.

Streptomycin and PAS was given the patient for five and one-half months before she became pregnant and during the entire pregnancy. She received a total of 179 Gm. during pregnancy. We are aware of the opinion expressed that streptomycin given during pregnancy may have an adverse effect on the infant, causing eighth-nerve deafness. For that reason many men withhold streptomycin during pregnancy or give it only in the last trimester. We have treated several patients with streptomycin during the entire duration of their pregnancies and have not noted any deleterious effects on either mothers or infants. Several of these infants are now over 2 years of age. Another objection to the use of streptomycin during pregnancy has been that the patient will become streptomycin fast and will not respond to this drug at a later date. In this patient the streptomycin was apparently effective for 18 months as evidenced by the clearing of the lesion on the left side.

Conclusion

1. A lobectomy performed for pulmonary tuberculosis in the first trimester of pregnancy is reported.

2. The lobectomy had no deleterious effect on the course of the pregnancy.

3. Labor and delivery progressed normally and both mother and infant are in excellent condition four months post partum.

4. The pregnancy did not adversely affect the improvement of the tuberculous process.

5. The patient received streptomycin and para-amino-salicylic acid before becoming pregnant and for the entire course of her pregnancy.

6. No ill effects from the continuous use of streptomycin during gestation were noted in the infant several months after delivery.

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98-11 Queens Boulevard, Forest Hills, N. Y. (Dr. Schaefer)
90-26 148 Street, Jamaica, N. Y. (Dr. Epstein)

THE USE OF HYALURONIDASE* IN EPISIOTOMIES†

J. E. Weber, M.D., A. M. Fetchko, M.D., and J. H. Carroll, M.D.,
Pittsburgh, Pa.

(From the Department of Obstetrics and Gynecology, Saint Francis Hospital)

PAIN following an episiotomy is probably the most frequent postpartum problem though few obstetricians have seriously considered it. The general opinion is that repair of an episiotomy will frequently result in pain regardless of precautions taken, and that a sedative and a local anesthetic ointment are sufficient. As additional treatment, an infrared lamp, hot compresses, Merthiolate spray, and sitz baths are occcasionally used. Reports of local infiltrations of the area with Eucupin-Procaine solution by Sheffery,[6] and Butecaine by Hunter[4] have not been received with enthusiasm.

Possibly Diethelm[2] and Mandy and associates[5] have more closely approached the solution by stressing the technique of repair.

We have noted that those patients who complain of pain have edema of varying degrees about the edges of the episiotomy. This may be due to birth trauma, trauma of the incision, sutures (possibly too tight), and infrequently sepsis. Since we believed pain and edema were associated, the diminution or elimination of the latter may solve the problem. Therefore, we have injected hyaluronidase along the edges of the episiotomy to reduce the degree of edema.

Procedure

Two hundred unselected cases were used for this study (Table I). One-half of these were obtained at random as controls. The types of episiotomy and repair were not planned—both midline and mediolateral episiotomies were used with continuous sutures in the muscle and skin; continuous in the muscle and continuous subcuticularly; interrupted in the muscle and continuous subcuticularly, and interrupted in the muscle and interrupted subcuticularly. Only the types of skin repair were recorded for clarity in Tables I and II.

Table I

	HYALURONIDASE	CONTROL
Multiparas	58	54
Primiparas	42	46
Left mediolateral episiotomy	67	64
Median episiotomy	33	36
Continuous	7	18
Subcuticular	85	65
Interrupted	8	17

Four hundred units of hyaluronidase were mixed in 1 c.c. of sterile water and placed in a tuberculin syringe with a 24 gauge hypodermic needle attached.

*We would like to thank G. D. Searle & Company for the generous supply of Alidase used in this experiment.

†Read before the Pittsburgh Academy of Medicine, May 13, 1952.

The needle was then inserted to its hub just beneath the raw skin edge of the repaired episiotomy and 0.1 c.c. injected at five equidistant points along either side.

The following day and each successive day until discharge these patients were questioned and examined. They were not told of having had an episiotomy unless it was insisted upon. Our introductory question was: "Do you have any aches or pains?" We were interested in knowing if there was pain, to what degree, and exactly where it was located. On examination we looked for hemorrhoids, the degree of edema about the incision, and union of the episiorraphy.

TABLE II

	HYALURONIDASE	CONTROL
EDEMA		
Total number of cases	8	24
Episiotomies.—		
Median	9%	13.9%
Left mediolateral	7.5%	29.6%
Repairs.—		
Subcuticular	8%	25%
Interrupted	12.5%	29%
Continuous	0%	16.6%
PAIN		
Total number of cases	19	39
Episiotomies.—		
Median	15%	30.5%
Left mediolateral	21%	43.7%
Repairs.—		
Subcuticular	17.5%	43%
Interrupted	25%	29%
Continuous	28.5%	33%
Edema and pain	5	17
Edema, no pain	3	7
Pain, no edema	14	22

Results

There was a significant difference in the number of patients having edema about their episiotomies in the hyaluronidase and control series. Eight per cent of the patients had edema in the former group and 24 per cent in the latter. Midline episiotomies produced edema in 9 per cent and 13.9 per cent; left mediolateral episiotomies in 7.5 per cent and 29.6 per cent, respectively. Clinically, we believed subcuticular repair was the most satisfactory, but were mildly surprised to find that continuous suturing produced less edema in both series (Table II).

We noted, too, that there were 20 per cent more patients who had pain in the control series and, as was expected, midline episiotomies caused less pain than left mediolateral episiotomies. It was presumed, based upon our original premise, that continuous repair would cause less pain, but this was not the case. Actually, it gave more discomfort in the hyaluronidase series, while the subcuticular repair was the worst offender in the control group. There was also a 12 per cent higher incidence of associated pain and edema in the control series. It was interesting to note that in both series pain occurred more frequently without edema (Table II).

Comment

Our original premise was based on the supposition that the presence of edema about the episiotomy placed tension upon the sutures and thus produced pain. Therefore, if the edema could be relieved the pain would be minimized.

The results presented do not uphold this assumption. As shown in Table II, pain was present without edema in many more cases than it was with edema, demonstrating that edema was usually not the etiological factor. Since this is true, the elimination of edema cannot justifiably be given as the reason for the reduction of pain.

Despite this fact, there is a significant reduction of edema and pain in the hyaluronidase series. We are unable to explain this or locate the factor or factors which are responsible unless hyaluronidase has an action of which we are unaware.

Another interesting phase of this study was the problem of wound healing. Cole and collaborators[1] brought to light a theory by Meyer on wound healing: "Young growing fibroblasts secrete hyaluronic acid which is followed by the secretion of chondroitin sulfate and of a precursor of collagen, the latter a nonfibrous and soluble protein. By local acidification in the immediate neighborhood of the fibroblasts the precursor is denatured by the polysaccharides, the latter acting as anionic detergents rolling up the peptide chains along the acidic groups of the fibrous polysaccharide molecules. Most of the hyaluronate is removed enzymatically, leaving the more firmly bound chondroitin sulfate as a network on the surface of the fibers. The latter by cross-linking grows into mature insoluble fibers."

Also McClean in 1942 discovered a factor in serum which inhibits hyaluronidase. This serum inhibitor was found to be present at the site of a wound and was increased in postpartum patients.

Since hyaluronidase was injected along the wound edges, an unknown amount of serum inhibitor would be utilized, which ordinarily would be used in normal tissue repair. Thus we were concerned about poor wound healing in our procedure. The results showed two episiotomy breakdowns in the hyaluronidase group and one in the control group with approximately equal healing qualities throughout both series. The fact that, as stated before, serum inhibitor neutralizes hyaluronidase would lead one to wonder how edema could be dispersed. Of course if there was an excess amount of hyaluronidase this dispersal would be possible, but again it would interfere with wound healing.

The amount of hyaluronidase used may not have been significant in this respect, but the use of larger doses on an experimental basis deserves investigation.

Summary

We have found 16 per cent fewer patients having edema and 20 per cent fewer having pain in the hyaluronidase series than in the control series, but this cannot be completely attributed to the use of hyaluronidase because pain was not caused by edema in a large number of cases. Possibly there are other factors present or an unknown action of hyaluronidase influencing these results. It was also found that hyaluronidase did not materially affect wound healing.

In the light of these results we are unable to recommend the use of hyaluronidase routinely in episiotomies, but suggest that it may be of value where an excess of edema is anticipated.

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UTERINE BLEEDING IN PELVIC INFLAMMATORY DISEASE

WILLIAM L. SMILEY, M.D., AND WILFRED BOZEMAN, M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Homer G. Phillips Hospital)

ABNORMAL uterine bleeding is one of the frequent conditions which will motivate a woman to seek medical care. This has become increasingly true during recent years, due to the recognition given this sign as a possible indication of malignant disease. In most general clinics, many women with such a complaint will be found in the premenopausal age group. Listing of the etiological factors responsible for bleeding in such a group usually includes in order of frequency:

1. Pregnancy complications
2. Inflammatory disease of the adnexa
3. Benign neoplastic disease
4. Functional bleeding
5. Malignant disease of the uterus

Acknowledgment of these conditions as being of importance in the causation of uterine bleeding is atested to by the voluminous literature in each of these various categories. There is a notable exception, however. This is uterine bleeding due to inflammatory disease of the pelvic organs. There is some justification for this in that, whatever the mechanism, the bleeding is secondary to inflammation and is seldom a serious threat to the patient's life.

Witherspoon,[1] many years ago, stated that pelvic inflammatory disease was the second most frequent cause of uterine hemorrhage in women of childbearing age. Fluhmann[2] in 1931 reported several factors which he felt would be involved in the production of so-called inflammatory uterine bleeding. They were:

1. Malposition and adhesion of the uterus with abnormal uterine contractility
2. Inflammation of the endometrium
3. Pelvic congestion
4. Chronic perioophoritis and congestion
5. Abscesses of the corpus luteum

Swinton and Blackwell[3] stated that this type of bleeding was due to endocrine imbalance as a result of ovarian dysfunction. Ward[4] attributed the cause to pelvic hyperemia and ovarian dysfunction.

In the Gynecological Clinic at Homer G. Phillips Hospital, irregular uterine bleeding due to pelvic inflammatory disease is a common finding. Because of the frequency with which such a diagnosis has been made and the relative paucity of information concerning it in the literature, further study of the condition seemed justifiable. To this end a study of the endometrium in patients presenting this symptom complex has been carried out.

Material

The patients for this study were obtained from the Gynecological Service. Twenty-one per cent of all persons in whom the diagnosis of pelvic inflammation was made exhibited irregular uterine bleeding. Forty such patients were selected with these qualifications:

1. All were bleeding or had within the last thirty days presented irregular uterine bleeding.
2. There were acceptable clinical findings denoting pelvic inflammation.
3. There were no demonstrable uterine myomas, polyps, or other anatomical causes of bleeding.

The ages ranged from 15 to 36 years; 35 per cent were nulliparous. The over-all duration of disease ranged from three weeks to four years. Sixty-five per cent gave histories of previous attacks of pelvic inflammatory disease. Fifty-five per cent had previous episodes of menstrual irregularity attributed to inflammatory disease. Twenty-six of those studied were bleeding at the time of biopsy, the duration of bleeding varying from twelve hours to forty days. Fourteen biopsied had not bled in the last ten to eighteen days; six presented moderate degrees of retrodisplacement. The types of bleeding as described by the patient is shown in Table I.

TABLE I

Metrorrhagia	22
Menometrorrhagia	8
Polymenorrhea	4
Menorrhagia	4
Oligomenorrhea	2
Total	40

Procedure

Inasmuch as all of these patients were felt to be in an acute or subsiding phase of inflammatory disease, they were all started on the usual conservative measures including antibiotic and/or chemotherapy for at least twenty-four hours prior to biopsy. The biopsy was obtained with the Novak suction curette, one stroke usually being adequate. The material was sent to the laboratory for pathological study. The results as reported are shown in Table II.

TABLE II

ENDOMETRIAL PHASE	BLEEDING	NON-BLEEDING
Proliferative	18	10
Secretory	4	0
Menstrual	2	0
Glandular hyperplasia	2	4
	26	14

Results and Comment

Of the patients who were bleeding at the time biopsy was performed, twenty, or 76 per cent, showed evidence of the proliferative phase in the endometrium. Six exhibited a secretory type of mucosa. Of the fourteen who were not bleeding at the time of biopsy, yet in whom the interval of time since last bleeding was sufficient for corpus luteum formation, not one showed evidence of secretory activity. For the combined series of women presenting

irregular bleeding incident to pelvic inflammatory disease, 85 per cent at the time of biopsy presented a nonsecretory type of endometrium, the histological pattern being very similar to that frequently found in patients labeled as having functional uterine bleeding. It is noteworthy that in no instance was a report of endometritis returned by the pathologist. Fifteen per cent incidence of retrodisplacements is well within the average found in pelvic inflammation not associated with irregular bleeding. It would seem from these results that the irregular bleeding frequently encountered in pelvic inflammatory disease results from or is associated with a failure of ovulation. This ovarian dysfunction is usually temporary and of wide variation in time of duration. It does not necessarily persist even during periods of clinical activity of the inflammatory process. This view is supported by two observations: (1) the preponderance of nonsecretory endometrium found at time of bleeding, and (2) the failure to find evidence of progesterone stimulation after cessation of bleeding at a time that ovulation would normally be expected to have occurred.

The relatively few cases of glandular hyperplasia suggest that not only is there a failure of ovulation but also some depression in follicular activity so that the endometrial response indicative of increasing estrogen titers does not obtain.

Clinical behavior of the bleeding is similar to that of so-called functional bleeding. Greenblatt and Barfield[5] state that, from a therapeutic standpoint, these patients may be treated for the bleeding with the same measures as are found successful in primary functional bleeding.

It seems likely, then, that in some cases of pelvic inflammatory disease, a disturbance of ovarian physiology results, manifested by irregular uterine bleeding, this disturbance being in the nature of failure of ovulation.

Summary

Forty cases of irregular uterine bleeding occurring in patients with pelvic inflammatory disease were studied by endometrial biopsy. Biopsies taken during bleeding and after cessation of bleeding revealed a preponderance of nonsecretory type of endometrium.

Conclusion

Irregular uterine bleeding coincident with pelvic inflammatory disease is probably due to ovarian dysfunction. In most instances, this results in a suppression of ovulation.

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Department of Case Reports
New Instruments, Etc.

KNOTHOLDER

ROBERT TAUBER, M.D., PHILADELPHIA, PA.

THIS new instrument* (Fig. 1.) has been designed to facilitate tying under tension. The distal end of this curved clamp has a conical shape, ending in a fine but blunt point, similar to that of a hemostat of the mosquito type. The important novelty, however, is that the insides of the blades are absolutely smooth, instead of having transverse or longitudinal crests and grooves. Thus, the suture material will not be damaged if the assistant holds the first knot in place while the surgeon ties the second knot with relaxed threads.

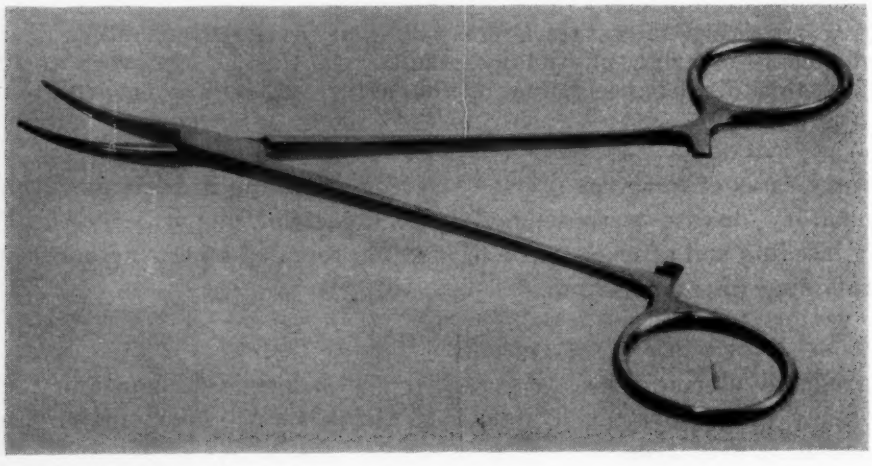

Fig. 1.

It is a special advantage that the instrument can readily be removed if the second knot is tied over one of the blades. The lock is simply opened and the smooth, conical blade is pulled out of the ligature loop. This manipulation does not do any harm to the suture ligature and does not weaken the knot.

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*Manufactured by Charles Lentz and Son, 33 South 17th St., Philadelphia 3, Pa.

FATAL CASE OF OBSTETRIC SHOCK DUE TO PULMONARY EMBOLI OF AMNIOTIC FLUID

DAN H. EAMES JR., M.D., GALVESTON, TEXAS

(From the Department of Obstetrics and Gynecology, John Sealy Hospital, University of Texas Medical Branch)

J. T., a 32-year-old Negro gravida vi, para iv, was admitted to the Obstetrical Service of John Sealy Hospital at 12:30 A.M. on Jan. 10, 1952 (Unit History No. 1057A, Autopsy No. 8761).

She had four previous uncomplicated deliveries, the last in 1948. The patient was first seen with this pregnancy in September, 1951; all physical and laboratory findings were normal, including x-ray of the chest. There was a normal course in the prenatal visits with the blood pressure averaging about 108/70. The last menstrual period was April 4, 1951, and estimated date of confinement, Jan. 11, 1952.

The patient awoke about two and one-half hours previous to admission with strong contractions, and noticed her bed was wet (membranes ruptured?). Shortly thereafter she had a chill, and about this time expectorated bright red blood which had continued. On admission, uterine contractions were of one minute's duration, interval of two minutes, and strong in nature. Examination showed: right occipitoanterior position (?), station minus two, dilatation 2 cm., fetal heart tones 160, strong and regular, blood pressure 110/60, oral temperature 102° F., pulse 100, and respirations 21. Physical examination revealed only a slow oozing of blood from several areas of gums. The lungs were clear at this time.

About twenty minutes after admission the fetal heart tones became irregular, varying from 70 to 140 per minute. Uterine contractions were becoming more severe, and lasted for one minute at one-minute intervals. Thirty minutes after admission the blood pressure was 90/40; the patient was given Demerol, 100 mg., and Hykinone, 5 mg., and taken to the delivery room for vaginal examination. This revealed a frank breech presenting, station minus one, and dilatation of 4 cm. It was also noted that a small scratch on the perineum incurred during the perineal preparation was oozing blood, and it continued without cessation. The patient was returned to the ward and treatment instituted: (1) penicillin 100,000 units intramuscularly; (2) terramycin 500 mg. intravenously in 500 c.c. of 5 per cent glucose in distilled water; (3) Hykinone 5 mg. repeated.

2:30 A.M. Contractions were of two minutes' duration, intervals of fifteen seconds, extremely severe. Fetal heart tones were very irregular. Blood pressure was 80/40. It was not felt that the bleeding from the gums was sufficient to account for lowering blood pressure; no other bleeding was visible and the patient was rational and cooperative. She had no complaints other than pain from contractions.

3:00 A.M. Blood pressure and picture were unchanged except that fetal heart tones were becoming faint. Active interference was not felt justified.

3:15 A.M. Dilatation was 9 cm. Blood pressure was 90/70. The patient was taken to the delivery room.

3:40 A.M. While she was being expectantly watched, the respirations suddenly became noisy and obviously "wet." Simultaneously, the respiratory rate visibly increased,

and moderate dyspnea and cyanosis were noted. Examination revealed gross moist râles over the posterior lower one-half of the chest. Pudendal block was done while emergency medical consultation was obtained. The diagnosis was "Acute pulmonary congestion and acute left ventricular failure." The patient rapidly became worse, and uterine contractions lightened. Respirations were about 30, pulse about 120, and blood pressure uncertain. She appeared to be in severe shock.

4:20 A.M. The internist felt the patient was in a very critical condition and advised extraction of the fetus if possible. A difficult breech extraction of a dead fetus was completed at 4:55 A.M. The weight was 8 pounds, 15 ounces. The placenta was delivered immediately and the uterus responded well to ergotrate with an estimated blood loss of 200 to 300 c.c.

At 5:24 A.M. the patient suddenly stopped breathing and died. She had oxygen by pressure mask continuously from about 3:50 A.M.; morphine, 16 mg., and Coramine, 1.5 c.c. at 4:40 A.M.; Cedilanid, 0.4 mg., at 5:10 A.M.; and Adrenalin 1:1,000 solution, 1 c.c., intracardiac at 5:25 A.M.

Laboratory Results.—

Blood Count: Hemoglobin, 12.7 Gm., red blood cells 5.72 million, white blood cells 21,200, neutrophils 65, stab forms 20, lymphocytes 15.

Clotting Time: In two and one-half hours none of the blood in any of the three tubes had clotted, or showed a tendency to clot. Upon standing, the cells settled to the bottom leaving a serum which had an orange opalescent murky color. Upon inverting the tube the cells immediately resuspended themselves and no evidence of clot formation was noted.

Postmortem.—

Only relevant gross and microscopic findings are given: (1) pleural effusion, right 300 c.c. and left 200 c.c., of a dark brown fluid; (2) pericardial effusion, 20 c.c. of dark fluid; (3) ascites, 200 c.c. of blood-tinged transudate; (4) numerous small subperitoneal hemorrhagic areas; (5) gastrointestinal hemorrhage, 200 c.c. of dark unclotted blood in stomach, dark tarry material in lower colon; (6) lungs, rubbery and filled with edema fluid, right 550 Gm., left 425 Gm.; (7) bronchi, slightly blood-tinged fluid present; (8) myocardium, flabby, and right ventricle markedly dilated. Weight 300 grams.

On microscopic examination of the lungs with hematoxylin and eosin stains, there was abundant evidence of amniotic fluid emboli in the small arterioles, and many of the capillaries were filled with the emboli. The picture was consistent with previously reported cases. Some of the smaller capillaries were filled with the typical epithelial squamae which stained lightly basophilic. The small arterioles demonstrated epithelial squamae in conjunction with red blood cells and some inflammatory cells. There was little amorphous debris found.

Mucin stains were negative which might possibly be explained on the basis of the fetal presentation, as the meconium had free passage from the uterus.

Fat stains were positive for the emboli.

Diagnosis.—Pulmonary embolism, amniotic fluid.

Comment.—In reviewing the literature of the cases reported I am unable to find any previous references to clotting time having been determined, or of any other blood studies having been done on these patients. Therefore it is not definitely established as yet exactly what the mechanism might be to produce this prolongation and the hemorrhagic tendencies so often noted in these patients.

In looking over this case several questions came to mind:

The entrance of the amniotic fluid into the maternal circulation is believed to be responsible for the hemorrhagic picture.[1] In this case bleeding from the mouth started over three hours before first evidence of drop of blood pressure, and five and one-half hours before visible signs of pulmonary congestion. Clotting time was obtained about an hour after the first drop in blood pressure and one and one-half hours before visible signs of pulmonary congestion.

Is there sometimes a latent period between entrance of amniotic fluid into maternal circulation and sudden appearance of severe symptoms—as a delayed type of anaphylactoid shock? Or are there—probably more likely—some small early emboli followed later by a large massive sudden showering?

In either event, if true, would a clotting time determination be of any benefit in early suggestive diagnosis in suspicious labors, i.e., those with extremely severe contractions accompanied by gradual unexplained fall in blood pressure as this patient had?

I wish to thank Dr. Yuan Tossi for his medical management and Dr. Bernard Rosen for his pathological study of this case.

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MULTIPLE PERITONEAL LEIOMYOMAS ASSOCIATED WITH A GRANULOSA-CELL TUMOR OF THE OVARY*

J. ROBERT WILLSON, M.D., AND AUGUSTIN R. PEALE, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology and the Department of Pathology, Temple University School of Medicine and Temple University Hospital)

UTERINE fibromyomas constitute the most common of the neoplasms arising in any organ in women and many attempts have been made to establish an etiological factor in their development. Since they appear only after the onset of ovarian function and since they usually regress after its cessation, it seems likely that some secretion from the ovary plays a part in stimulating the growth of susceptible uterine tissue. Witherspoon[1] has suggested that the tumors are the result of unopposed stimulation of the myometrium by the estrogenic hormone due to a failure of ovulation and corpus luteum development. This theory was suggested because he had encountered a high incidence of endometrial hyperplasia associated with fibroids and because Nelson[2] and Lipschutz and his co-workers[3, 4] had been able by repeated injection of the estrogenic hormone to produce tumors in animals similar to those developing "spontaneously" in the human being. This effect could be inhibited by the simultaneous injection of progesterone. Vargas, using oophorectomized monkeys, was unable to produce definite nodules with long-continued estrogenic treatment, but he did note pronounced myometrial and peritoneal fibrosis.

Because the phenomenon of peritoneal tumor growth associated with estrogen stimulation comparable to that produced in experimental animals has not previously been reported in the human being the following case is presented.

M. P., gravida 0, aged 38 years, white, and unmarried, was first seen on May 24, 1948, complaining of pressure in the pelvis, backache, and headache which had been present for about six months and which were gradually increasing in severity. She had also experienced frequency of urination and pain during bowel movements but constipation, which had been present for many years, was not increased.

Past History.—She had had an appendectomy at the age of 15 years, and subtotal hysterectomy for fibromyomas at age 27.

Menstrual History.—The menses were irregular at intervals of 3-6 months from the menarche at 16 years of age until the hysterectomy. The amount of flow was normal. Following the operation 2 day episodes of vaginal spotting had occurred at 28 day intervals. There had been no associated pain.

Physical Examination.—The abnormal findings were confined to the abdomen and pelvis. Right lower quadrant and lower midline surgical scars were noted and a slightly tender small mass was felt in the umbilical region.

On pelvic examination the external genitals were normal. The cervical stump was clean and was pushed anteriorly and immobilized by a firm, fixed, irregular midline mass about 10 cm. in diameter. In each lateral pelvic area was felt another firm irregularity measuring about 4 by 6 cm. Rectal examination confirmed these findings.

The patient was admitted to the hospital for laparotomy with a tentative diagnosis of carcinoma of the ovary.

Operation.—At laparotomy on May 29, 1948, the following gross findings were noted:

"Upon entering the abdomen a loop of bowel was encountered just to the right of the upper angle of the old incision. This was attached both to parietal peritoneum and to several large nodules in the omentum. The 'tumor' in the pelvis consisted of many nodules varying in size from ½ to 6-8 cm. in diameter. The largest of these arose from the cervical stump but the remainder were arising from the entire peritoneal area of the

*Presented at a meeting of the Philadelphia Obstetrical Society, Jan. 3, 1952.

pelvis. They appeared to be single and to arise from pedicles from the peritoneal surface. There was no evidence of invasion of the tissue in the pelvis or the bowel wall. The ovary on the right side was half again normal size and free, the left ovary was grossly normal. Both tubes were normal. The cervical stump was 5 cm. long and was freely movable.

"In the omentum were multiple nodules varying in size from 1-2 cm. to a size of 4-5 cm. These did not appear to be metastases from a malignant tumor; each tumor being an isolated nodule with the gross appearance of a benign fibroid. The omentum was normal, there were no enlargements of the retroperitoneal nodes or the liver."

The cervical stump, both tubes and ovaries, the omentum, and all the tumors except for a few small ones in the pelvis were removed. The postoperative course was uneventful except for distention relieved by Wangensteen's suction and the patient has since been relieved of her complaints.

Subsequent examinations have revealed no evidence of regrowth of the tumors. The patient now is asymptomatic except for constipation.

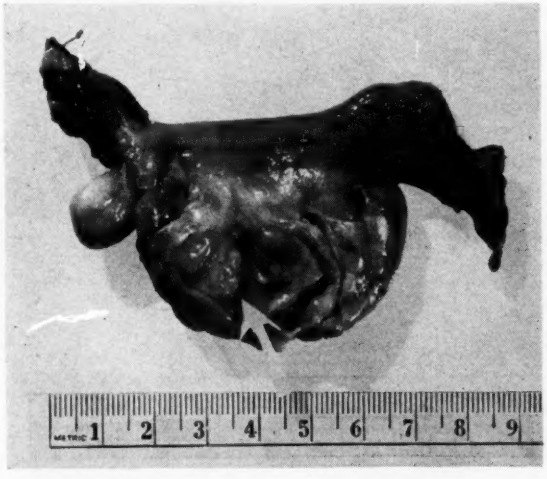

Fig. 1.—Arrow points to tumor in ovary. A fibroid mass can be seen to the left.

Pathology.—The initial pathologic study was of a frozen section of a firm, well-encapsulated, smooth tumor measuring 2.5 cm. in diameter which had the gross and microscopic characteristics of a benign leiomyoma. Because of the gross pathologic picture suggesting pelvic malignancy with metastatic spread, a second tumor was submitted for similar study with a similar benign evaluation, following which the surgical removal was carried out. The specimen was described as follows:

"The specimen consisted of the stump of the cervix measuring 5 by 3.4 by 2 cm. intimately attached to which there were roughly 15 fibroid masses, both Fallopian tubes, and both ovaries. One tube measured 10 cm. long; its accompanying ovary was enlarged and firm. The latter measured 5 cm. in diameter and at one pole there was a firm, yellowish-white lobulated tumor which resembled the fibroid masses in consistency and appearance (Fig. 1). At the opposite pole there was a corpus luteum. The opposite salpinx was tortuous and was adherent to its corresponding ovary. The ovary measured 3.5 cm. in diameter and was sclerotic. With the specimen there were nine loose fibroid tumors, two clusters of fibroid masses, and a piece of omental tissue which bore 36 similar tumors (Fig. 2). These tumors were well encapsulated, discrete and firm. They varied from 1 cm. up to 5.5 cm. in diameter. Upon sectioning, their cut surfaces had the characteristic appearance of uterine leiomyomas.

"Multiple sections were made of the fibroid masses and their microscopic pattern showed whorls of spindled cells with isolated neoplastic muscle bundles in solid nests

and islands (Fig. 3). All the cells were uniform in size, shape, and tinctorial reaction. Mitotic figures were not identified. Areas of hyaline alteration, necrosis, myxomatous degeneration and cyst formation disrupted the usual monotony of the interlacing bundles of smooth muscle cells in some of the sections. A few of the tumors revealed increased cellularity, but the morphology of these cells was entirely benign. Masson's, van Gieson's and Mallory's aniline blue stains revealed a predominence of smooth muscle elements. Scattered about the sections there were vascular channels.

"The cervical stump revealed thickening of the wall and moderate dilatation of the contained endocervical glands. A small fragment of endometrial tissue was identified at the upper level of the endocervical stump. The stroma was compact and lymphoid in appearance; the glands were increased in number and showed microcystic dilatation.

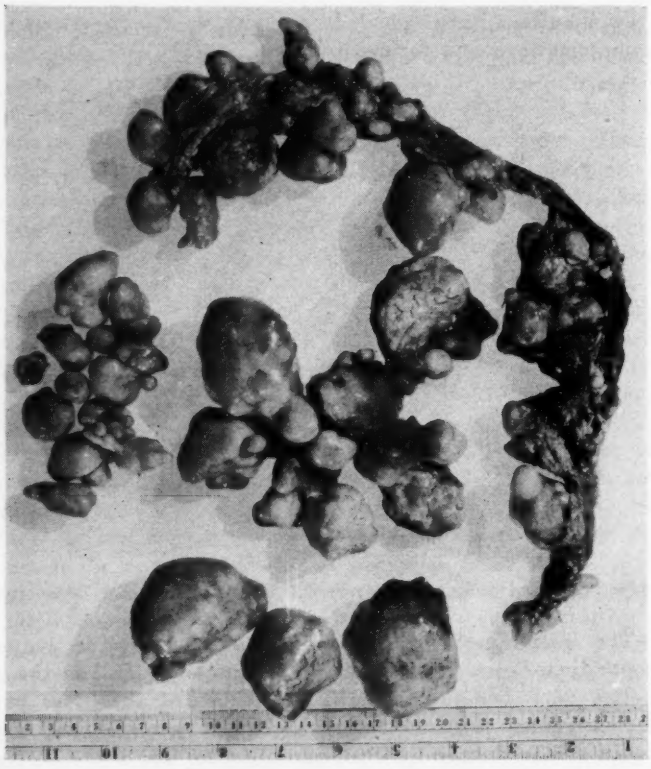

Fig. 2.—Clusters of fibroids, presenting a necklace-like pattern in the omentum.

There was no evidence of swiss-cheese hyperplasia. Unfortunately, the uterus had been removed at another hospital and we were unable to obtain an adequate section of the endometrium.

"One ovary contained a tumor which was quite classical for a granulosa-cell neoplasm (Fig. 4). Embedded in a dense hyalinized stroma there were masses of small blue-staining nuclei which possessed indistinct cytoplasm. The cells tended to be low cuboidal or ovoid. These cells in some areas had a haphazard arrangement, but in other places they had a plexiform or gyriform pattern and in still other areas they had a microfolliculoid grouping. While the majority of the cells were round or cuboidal, in a few areas they assumed a spindled character and were arranged in plaques or bundles. The opposite ovary was sclerotic and contained three germinal inclusion cysts.

"The histopathological diagnoses were multiple leiomyomas of the cervical stump, pelvis, and omentum, and granulosa-cell tumor of the ovary."

Comment.—The gross pathologic picture encountered in this patient was similar to that produced in certain experimental animals by continuous unopposed estrogenic stimulation. Although the operation was performed on the twenty-fourth day of the menstrual

Fig. 3.

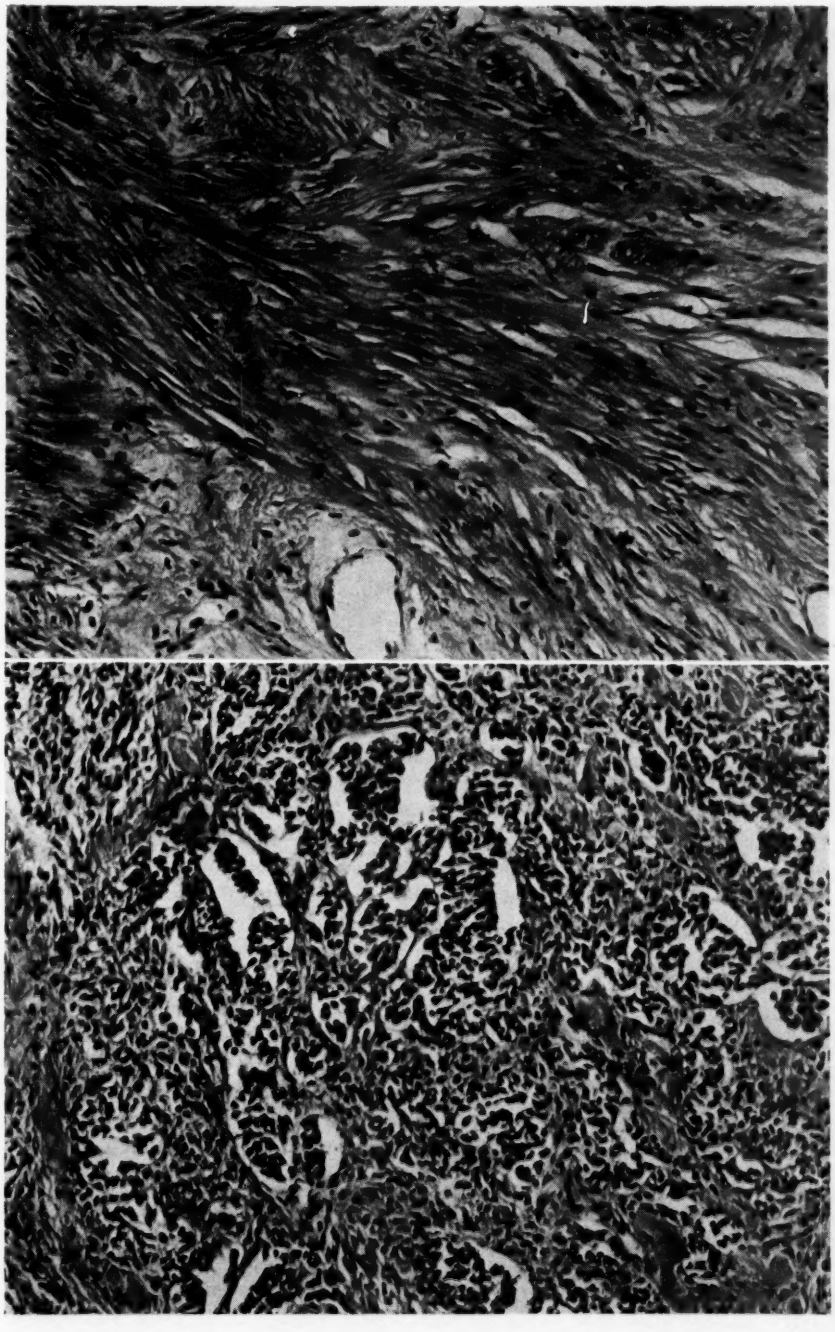

Fig. 4.

Fig. 3.—Low-power view of one of the fibroid masses. (Hematoxylin and eosin stain.)
Fig. 4.—Moderate magnification of the granulosa-cell tumor of the ovary.

cycle and a grossly normal-appearing corpus luteum was noted in the ovary there was no evidence of a progestational change in the remaining endometrium. This could result either from an estrogen level so high that the corpus luteum effect was not demonstrable or from the inability of the remaining endometrium to respond to the hormone. No evidence of hyperplasia was noted which, however, does not prove a low level of estrogen production.

The origin of the "fibroid" tumors in relation to the cervical stump is readily explained, but their presence in the peritoneum and omentum where there is no muscle warrants conjecture. Because of their multiplicity it does not seem likely that these tumors represent growths that had been weaned away from the uterus. They could, however, represent metaplasia of connective-tissue cells into smooth-muscle elements or adult differentiation of primitive mesenchymal cells, as a result of prolonged estrogenic stimulation. Perhaps, like the solitary cutaneous and subcutaneous leiomyomas as accepted by Stout,[5] these tumors arose from the smooth-muscle bundles of the blood-vessel walls. This concept has been recently affirmed for the development of leiomyomas in goldfish.[6]

The widespread development of benign leiomyomas over the surface of the peritoneum, the cervical stump, and the omentum in a patient with a granulosa-cell tumor is reported. It seems likely that this represents in a human being a duplication of the production of comparable tumors by prolonged unopposed estrogen stimulation in certain experimental animals.

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INTERMITTENT HYDRARTHROSIS

ROBERT I. HILLER, M.D., F.A.C.S., MILWAUKEE, WIS.

THE subject of intermittent hydrarthrosis has been summarized by Schlesinger,[1-4] Bierring,[5] Pulawski,[6] and Berger.[7] The first case was reported by Perrin in 1849[1] In 1921 Bierring summarized the literature and found a total of 77 cases. When Berger reported his case of allergic etiology in 1939, he was able to find a total of 105 cases. The average age incidence is between 20 and 45 years, but cases in much younger and older patients have been reported. Careful scrutiny of many of the cases reported discloses marked variation in the interpretation of the definition of the condition. It does not appear to be a disease entity, but has a varied etiology. Infection, allergy, trauma, and endocrine disturbances have each been described as responsible for its cause. Melane and Midana[8] were able to obtain a positive Frei Test with fluid obtained from the knee joint in three patients, who were Frei positive. The test was negative in three others, who were Frei negative. In a case of persistent hydrarthrosis, Poirier[9] obtained a positive agglutination reaction with the Flexner bacillus of dysentery in 1:600 dilution. The onset of hydrarthrosis was preceded by diarrhea and the fluid, though sterile, contained 60 polymorphonuclear leukocytes and 40 lymphocytes. Bierring[5] reported a case of a man 36 years old, who had a previous history of malaria, typhoid, and rheumatic fever. Nielson[10] reported a case of intermittent hydrarthrosis in a woman of 38 years who had attacks of joint swelling every 13 days. There had been a history of two attacks of rheumatic fever. There was no response to therapy.

Miller and Lewin[11] reported a case of a woman of 36, who responded to typhoid vaccine intravenously as a form of nonspecific therapy; and which was, therefore, considered to be due to anaphylaxis. Quincke's edema was considered the cause in some cases by Schlesinger.[1] He found cases in which the attacks were associated with either sialorrhea, edema of the glottis, or diarrhea. In one family, he found several members afflicted with intermittent hydrarthrosis. Quincke's edema was present in two affected members. Blood dyscrasia, probably purpura, was present in members of one of the afflicted families. Reimann and Angelides[12] also collected a group of cases of periodic arthralgia in five generations of one family. Several of the cases were in males. None of the women were relieved during pregnancy and many of the cases were described as showing "black and blue spots" about the joints involved. Weismann-Netter[13] reported a case of a woman 56 years old, whose effusion appeared with marked regularity with her periods. He made careful chemical analysis of fluid removed from the knee joint. He also studied the blood chemistry. He obtained a complete cure after seven injections of ergotamine tartrate following no results with thyroid, ovarian extract, atropine, Adrenalin, alkalization with sodium bicarbonate, acidification with acid phosphate, injections of peptone, autohemotherapy, Atophan, and intravenous calcium chloride. The first injection of ergotamine tartrate made the knee worse. Disagreeable side effects from the use of this drug were vomiting, less regular periods, and abdominal pain due to uterine contractions. Berger[7] also reported a case relieved by ergotamine tartrate.

Cases of endocrine etiology have been reported by several authors. In 1932 Rheindorf[14] reported two interesting cases: one started with intermittent hydrarthrosis with the onset of menses at the age of 13 years. At the age of 10, the paitent had had diphtheria with heart failure. With the onset of menses, fluid appeared in the knee, ankle, and hip, and later in the hand, elbow, and shoulder with each period. Her periods stopped for a while at the age of 14. Effusion also stopped. At age 15, following scarlet fever, the effusion became more severe. It was relieved by ovarian implant for six months. It was later also relieved by hypnosis. The second case was that of a woman

of 40 who had had intermittent hydrarthrosis since the age of 10. She had no effusion during five pregnancies. Both knees were affected. X-rays were negative. Her blood count and sedimentation rate were normal. The administration of estrogenic hormone caused disappearance of the effusion. However, one can draw no definite conclusions regarding the therapeutic value of estrogen in this second case because the amount commonly administered in 1932 was quite small. Schlesinger[2] believed that there was a definite relationship between effusions and ovarian dysfunction because they both frequently disappeared with the onset of the menopause. Some of his cases were treated with ovarian extract, roentgen sterilization, or placental extract. Beveridge[15] reported a case of intermittent hydrarthrosis starting in a woman 73 years of age. Schmitza[16] questioned the relationship of ovarian dysfunction to intermittent hydrarthrosis. Alonza[17] reported a case successfully treated with testicular extract. Lievre[18] reported relief of hydrarthrosis by the implantation of testosterone in a case of eunuchoidism. The 44-year-old man had been operated upon at age 5 and again at 11 for cryptorchidism. Intermittent hydrarthrosis had been present since the age of 41. Edema of the ankles was also present. He had many types of treatment, including x-ray therapy and several aspirations of the knee joints and injections of quinine and urea. His basal metabolism rate was minus 18, blood cholesterol was normal. Surgery was suggested but testosterone propionate injections and later the implanation of seven 100 mg. testosterone pellets beneath the skin of the abdominal wall caused disappearance of the joint effusions. Rebierre[19] reported three cases, in two females and one male, that were greatly improved with thyroid extract. In one case, however, that he was able to follow, symptoms recurred when thyroid was stopped and then failed to respond to reinstatement of the thyroid therapy.

Other means of therapy have also been tried. Krida[20] in 1933 reported two cases of intermittent hydrarthrosis apparently cured by synovectomy. Mandl[21] reported relief, but not cure, from synovectomy. Symptoms recurred but not as intensely as prior to surgery. Epstein and Edeiken[22] reported a cure with x-ray therapy. Pelner[23] experimented with low-salt and acid-producing diets with some results. Sodium bicarbonate increased effusion. He found the effusion in inflammatory arthritis to have an icteric index below 5. He found the traumatic effusion to contain red blood cells, leukocytes, and increased bilirubin due to hemolysis of the red blood cells, and mucin. The increased bilirubin content was found in the hemarthroses of hemophilia, sarcoma, xanthoma, and tabetic arthropathy.

Mrs. F. S., a white woman, aged 27 years, was first seen on Sept. 13, 1946, with the chief complaint of intermittent swelling of the right knee. The swelling occurred every 12 to 14 days and lasted from three to five days. In the interval between attacks, the knee was perfectly normal. Her periods occurred every 29 days and lasted 7 days without clots or pain. Further questioning disclosed that the swelling occurred just prior to and during the first two days of her menses, and again midway between periods. The swelling was accompanied by pain of a "pressure or bursting" type. Associated with this pain in the knee, she had moderate aching and drawing pains down the right leg. Aspiration of the knee joint revealed a large amount of amber fluid. Associated with the attacks, she had had throbbing frontal headaches. No demonstrable benefit was obtained from the use of penicillin, stilbestrol, autoinjection, pyribenzamine and chorionic gonadotropin. There was no history of allergy. X-ray examination of the right knee on three occasions disclosed no bony abnormality. During pregnancy in 1948, and during the period of lactation which followed her delivery, there was no swelling of the knee. Tonsillectomy was performed in childhood and again at 17 years of age. She developed tetany following the second operation.

Physical examination disclosed a well-developed and well-nourished white woman, who did not appear acutely or chronically ill. The skin showed a mild seborrhea. The pupils of the eyes were equal and reacted to light and accommodation. Extraocular movements were normal; there was no exophthalmos. The fundi were normal. The nose, ears,

and mouth disclosed no abnormalities. The tonsils had been removed. The thyroid was just palpable. There was no bruit and the cervical lymph nodes were not enlarged. The breasts were normal. The lungs were clear. The heart had a regular rhythm. No murmurs were noted. The rate was normal. The abdomen presented no tenderness, fluid, or masses. The liver, spleen, and kidneys were not palpable.

Pelvic examination revealed a two-finger introitus. The cervix was not visible nor palpably diseased. No discharge was present. Two fibroid tumors each about 2 cm. in diameter were palpable on the fundus. The adnexa were negative to palpation.

Rectal examination was negative.

The deep reflexes were equal and active. The blood pressure was 120/70.

During an attack the following measurements of the knees were noted:

	RIGHT	LEFT
Suprapatellar circumference	15½ inches	14½ inches
Transpatellar circumference	14¾ inches	14 inches
Infrapatellar circumference	12½ inches	12 inches

After the attack subsided measurements of 14, 13¾, and 12¼ inches were noted on the right. The quadriceps muscle showed slight atrophy.

At the Mount Sinai Hospital, in New York, where she was finally sent for a thorough investigation and for an opinion on the use of testosterone, the orthopedic consultant discovered a small Baker's cyst in the popliteal space of the right knee. He recommended removal of this cyst if no success was achieved by other means. Examination by the consulting allergist disclosed negative sensitivity tests except for dust. The laboratory findings were as follows: *Blood examination:* hemoglobin 13.0 Gm., leukocytes 9,150 of which the polynuclears constituted: segmented 44 per cent, stab forms 8 per cent, lymphocytes 44 per cent, eosinophils 1 per cent, basophils 1 per cent, monocytes, 2 per cent. The sedimentation rate was 12 mm. in one hour, normal. The Kahn test for syphilis was negative. The Blood Wassermann test was negative. Blood uric acid was 2.0 mg. per 100 c.c. (normal 2 to 3 mg.). The urine was clear, acid, with no albumin or sugar, specific gravity 1.030, and microscopic examination of a centrifuged specimen showed occasional epithelial cells, yeast, rare white blood cell. The basal metabolic rate was minus 19 per cent, pulse 76. Electrocardiogram showed T4 semi-inverted, no significant abnormalities. X-rays of both knees showed no abnormality in the bones, joints, or adjacent soft tissues. Culture of the knee joint fluid showed no growth. A trial of x-ray therapy was suggested by one of the consultants. He also thought that the testosterone therapy could be tried.

Upon her return from the examination at the Mount Sinai Hospital in New York, she was given one injection of 500 units of A.P.L. (chorionic gonadotropin) followed by aggravation of the swelling of the knee. On June 16, 1949, 25 mg. of testosterone propionate were given intramuscularly. It was repeated at intervals of two weeks. Thyroid extract, 1½ grains daily, was taken orally by the patient. The injections were finally timed to precede ovulation and menstruation, and the swelling disappeared completely after a period of approximately three months. Injections were stopped completely on Feb. 20, 1950. There has been no recurrence of the pain or swelling. She has, however, continued to take the thyroid extract nearly every day.

Discussion.—Because the condition was aggravated by the administration of stilbestrol, the question of sensitivity of the patient to her own estrogen arose. However, swelling of the knee was present at ovulation time when the estrogen level is ordinarily high and also at menstruation when it should be low (Smith and Smith[24]). The swelling was absent during pregnancy when the estrogen level is very high, and during lactation when the level is very low (Goldberger[25]).

The patient has Rh-negative blood. She has two sisters, one Rh negative and one Rh positive. Her husband has Rh-positive blood. Her older child, a boy, has Rh-negative blood.

Consequently the possibility of sensitization to her child's blood during her first pregnancy as a factor in the etiology of the intermittent hydrarthrosis is ruled out. Her symptoms disappeared during her second pregnancy with an Rh-positive girl.

Since the thyroid activity during pregnancy and lactation should not vary appreciably from the patient's normal, the use of thyroid extract could not be credited with her improvement, in spite of her minus basal metabolism. The testosterone would, therefore, appear to be the therapeutic agent responsible for her cure.

Hellbaum, Ishmael, and associates[26] from the University of Oklahoma have reported encouraging results from the use of testosterone in the treatment of rheumatoid arthritis in 57 per cent of 124 cases treated.

Summary

A case of intermittent hydrarthrosis is presented which responded to testosterone therapy. Symptoms also disappeared during pregnancy and lactation.

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208 East Wisconsin Avenue

PLACENTA PREVIA OF THE SUCCENTURIATE LOBE

ORVAN W. HESS, M.D., F.A.C.S., NEW HAVEN, CONN.

(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)

AMONG the variations of the gross form of the human placenta, an accessory, or so-called succenturiate, lobe is not infrequent.[1] When careful examination of such an abnormal placenta is made following delivery, one or more lobules may be found attached to the layers of the amniotic membrane and entirely separate from the periphery of the main body of the placenta. These discrete portions of placental tissue are commonly connected by well-developed blood vessels.

Such abnormalities may occasionally assume clinical significance of great practical importance. Even when meticulous inspection of the placenta after delivery has been carried out, a succenturiate lobe may be overlooked and retained in utero following the expulsion of the main placenta. This may result in uterine atony, postpartum hemorrhage, and potential infection. Large vessels connecting the aberrant lobe with the main placenta may traverse the internal os (vasa previa) and, in the course of labor, rupture with ensuing hemorrhage endangering the infant.[2, 3] Perhaps more frequently the succenturiate lobe may be implanted low in the vicinity of the internal os (placenta previa) with the likelihood of premature separation and attendant hemorrhage during labor. The following case, which demonstrates this complication, was encountered on the obstetrical service of the New Haven Hospital.

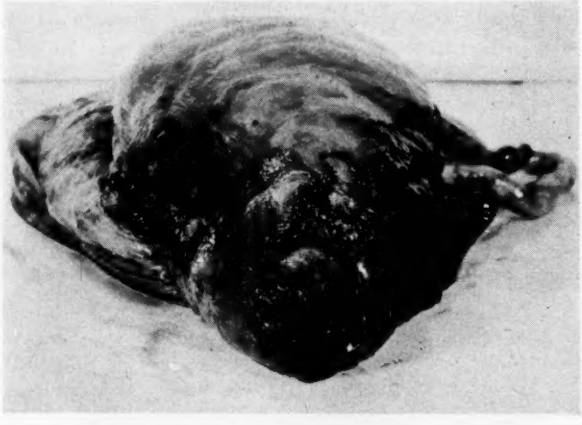

Fig. 1.—Uterus showing position of attachment of succenturiate lobe in vicinity of os uteri.

Mrs. R. F. E., white, married, aged 40 years, was first seen during the third month of her second pregnancy. Past history revealed that her first pregnancy, three years previously, had terminated in a premature labor following spontaneous rupture of the membranes. The infant, a male approximating 1,650 grams, survived. Except for a cervical polypectomy and tracheloplasty, the remainder of the history was noncontributory. General physical examination was negative. Pelvic examination showed a marital introitus with cystocele, the cervix soft and flattened. The uterus was symmetrically enlarged 2 to 3 cm. above the symphysis pubis, soft, and slightly tender. The cervical os was small, 3 to 4 mm. in diameter, while the endocervix was discernible as a ridge only slightly elevated above the adjacent mucosa of the vaginal vault. The blood pressure was 140-120/80-60; urine negative; Kahn test negative; blood Rh positive; chest film negative; Aschheim-Zondek test positive. Pelvimetry (Thoms) showed the pelvis to be adequate, dolichopellic.

Fig. 2.—Fetal surface of placenta demonstrating two succenturiate lobes and intervening blood vessels.

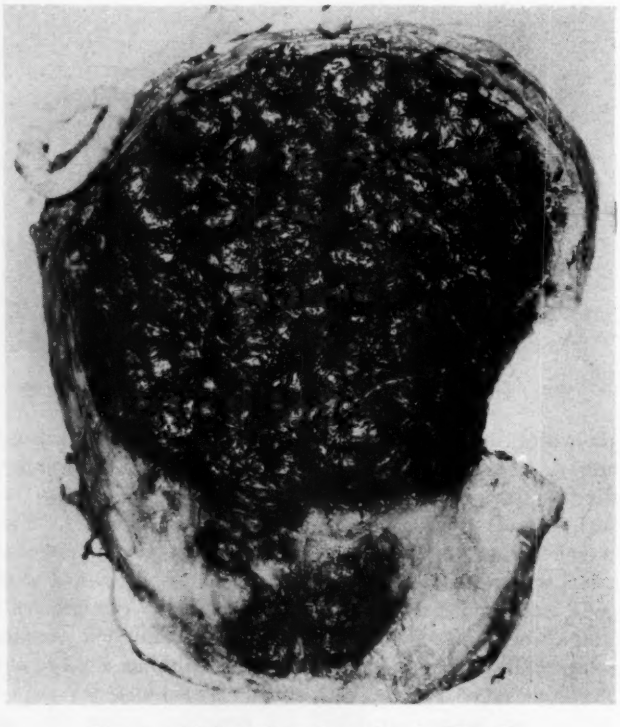

Fig. 3.—Maternal surface (as in Fig. 2).

The course of the gestation was complicated by episodes of suprapubic discomfort and tenderness suggestive of chronic pelvic inflammatory disease as well as by an anxiety neurosis. The weight gain was 21 pounds.

The patient was admitted March 27, 1950, to the New Haven Hospital near term following the onset of sharp, intermittent lower abdominal pains occurring every five minutes. Abdominal examination revealed the vertex engaged, position left occipito-transverse, fetal heartbeat 130, in the left lower quadrant. Rectal examination showed the vertex above the ischial spines, and the cervix indefinite but considered to be about 2 cm. dilated. Rectal palpation was unsatisfactory; consequently, five hours later, sterile vaginal examination was done. The cervical os could not be made out. A speculum was introduced to expose a thin rim which felt like edematous cervical tissue contiguous with the vaginal wall. The patient was returned to her room and, after several hours, re-examination revealed a somewhat more definite ring of edematous tissue, approximately 3 cm. in diameter, in the region of the cervix. This appeared to be occluded by a band of what might be presumed to be scar tissue in the center of which there appeared to be a small orifice 1 to 2 mm. in diameter. This was gently dilated with a curved clamp. The amniotic sac was thought to bulge slightly through this site. Labor continued with episodes of strong, sustained contractions without progress for approximately four hours. Vaginal palpation was repeated and large blood clots were removed followed by fresh bleeding (100 to 150 c.c.). The edematous ring was felt to be approximately 4 cm. in diameter and about its margin soft, spongy tissue was readily discernible. In view of the finding of placenta previa associated with active bleeding, immediate cesarean section was performed. A male infant in good condition was delivered. The entire uterus was then removed with the placenta in situ. This operative procedure was very well tolerated by the patient. The postpartum course was uneventful and the patient was discharged from the hospital on the eighth postoperative day.

Examination of the placenta and uterus (G16220) after total hysterectomy disclosed the placenta to consist of the main body and two succenturiate placental lobes approximately 5 cm. and 3 cm. in diameter, respectively. These aberrant lobes, attached by intervening membranes and large blood vessels to the main placenta, were found to extend across the vicinity of the internal cervical os with the margin of one lobe showing evidence of pre-existing, recent detachment as a source of bleeding.

Comment.—

1. The finding of placenta previa involving two succenturiate lobes noted after cesarean hysterectomy is herein recorded.

2. Until improved methods of diagnosis have been perfected, management should be largely that of placenta previa involving the main placenta.

3. When removal of the uterus is indicated following cesarean section for placenta previa, complete hysterectomy is advisable to avoid postoperative bleeding. In most cases this can be done with little risk to the patient.

4. The frequent observation of low implantation of the placenta, or frank placenta previa, where deep lacerations of the cervix have been known to exist, or extensive tracheloplasty has been done, suggests the possibility that such trauma may predispose to subsequent placental attachment in that area. Effort should be made to determine the location of the placenta before onset of labor among such patients.

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79 Trumbull Street

Department of Reviews and Abstracts

Selected Abstracts

Abortion

Rodriguez, Fernando, and Oneto, Jose: Negation of Therapeutic Abortion in Pulmonary Tuberculosis, Bol. Soc. chilena de obst. y ginec. **16:** 11, April, 1951.

In 1945 one of the authors reported on the evolution of pulmonary tuberculosis in 31 cases in which the pregnancies had been interrupted; there was frank aggravation of the tuberculosis in 42 per cent, and only 29 per cent improved.

Since then the authors have had the opportunity of observing and following up 14 cases in which therapeutic abortion was refused. These patients had all types of pulmonary tuberculosis, except miliary tuberculosis. Some were active cases and others quiescent. All were under periodic control or received treatment when indicated (rest at home or in the hospital, pneumothorax where indicated, etc.). Streptomycin was not used.

All active cases showed regression of the lesions during gestation, with the exception of one case in which the disease was already far advanced. The inactive or arrested cases showed no change during pregnancy.

In 11 cases the pregnancy went to term, in one instance to 8½ months, and in 2 cases to 8 months. All babies were living and apparently well and none of the mothers suffered any apparent ill effects from their pregnancies.

Twelve patients were followed up after delivery. In only one (the patient with far advanced tuberculosis) the disease continued to progress. All the others continued to improve, or remained stationary as they had during pregnancy.

The authors conclude that therapeutic abortion for pulmonary tuberculosis is not justified in patients who are under periodic control and/or treatment. MAGIN SAGARRA.

Bishop, P. M. F., and Richards, N. A.: Habitual Abortion, Further Observations on the Prophylactic Value of Progesterone Pellet Implantation, Brit. M. J. **1:** 244, Feb. 2, 1952.

The authors present an additional series of 40 patients with histories of habitual abortion (two or more) treated by implantation of 150 mg. of progesterone, as early as possible in the current pregnancy. These cases are combined with a previous series of 45 cases. From the total number of 85 cases, 85 per cent had live births when two previous miscarriages had taken place, and 72 per cent when three or more spontaneous abortions had occurred. The psychotherapeutic effect of the implantation is mentioned.

The authors mention the excellent results obtained by Bevis (Lancet **2:** 207, 1951) who had 81 per cent success in the management of 32 of these patients without endocrine therapy. CARL T. JAVERT.

Anesthesia, Analgesia

Palliez, R., Cotteel, P., and Delecour, M.: A Clinical Study on Trial of Trilene Anesthesia in Obstetrics, Bull. Féd. Soc. de gynéc. et obst. de lang. franç. **3:** 631, 1951.

The authors employed Trilene as a patient-administered anesthetic agent in 100 consecutive labors. Twenty-three of the patients were primiparous. The Trilene was

begun at a dilatation of 3 to 5 cm. The Trilene neither altered the contractions nor prolonged the labors. The expulsive phase was practically painless. Forceps were required in only 4 cases. The recovery was rapid, easy, and without side effects. The authors found no indication of toxic side effects in either mothers or infants. The authors state its use should be restricted to the better hospital, however. A discussant, Gelle, points out that Trilene exhibits certain hazards and inconveniences somewhat similar to those seen with ill-used chloroform.

CLAIR E. FOLSOME.

Cancer, Malignancies

Dickstein, Alice: Sarcoma of the Uterus, An. brasil. de ginec. **32:** 159, Oct., 1951.

The author collected seven cases of sarcoma of the uterus over a fifteen-year interval, 1936 to 1950, inclusive, from the files of the Gynecological Clinic of de Moraes at the University of Brazil. In this interim she notes there were also 387 myomatous uteri, hence an incidence of 1.8 per cent of sarcomatous uteri. The author concludes by stressing the need for more periodic pelvic examinations. Six photomicrographs accompany the article.

CLAIR E. FOLSOME.

Todd, Margaret C.: The Place of X-ray Therapy in the Treatment of Malignant Ovarian Tumours, J. Obst. & Gynaec. Brit. Emp. **58:** 385, 1951.

X-ray therapy in the management of ovarian malignancy has been employed for many years, yet there is little accurate knowledge of its value. It is always difficult to ascertain with any degree of accuracy the final effect of the x-rays, either pre- or postoperatively. The surgeon may perform total hysterectomy, with wide lateral dissection, and believe he has removed all malignancy, to find later that he did not. Tissue outside the operative field has already become infiltrated microscopically, if not macroscopically, with malignant cells. Postoperative x-ray is given, but just how efficacious it is is very difficult to determine. Take another case where the tumor is apparently confined to the ovary or ovaries, panhysterectomy removes all the malignancy, x-ray therapy is given, and the patient is cured. How do we know but that panhysterectomy alone might have effected a cure? It is most difficult to assess the true value of any one procedure in the treatment of cancer; consequently both x-ray and surgery are indicated. The author's five-year crude survival rate was 30 per cent in 125 cases treated in the Holt Radium Institute in Manchester, England. Results by pathological group were best in adenocarcinoma, 47 per cent of 27 cases, and in papillary cystadenocarcinoma, 44 per cent of 27 cases; thus 54 cases of the more common types of ovarian malignancy had a five-year crude survival rate of 46 per cent, which is excellent. Only by the cooperative collaboration of roentgenologist and surgeon can such results be obtained.

HARVEY B. MATTHEWS.

Cesarean Section

Trân-Dinh-Dê: Remarks Concerning a Series of 282 Cases of Abdominal Cesarean Section Gynéc. et obst. **49:** 400, 1950.

The author reviews a series of cesarean sections performed at the George Béchamp Maternity Hospital of the Saigon Medical School, Thailand. The survey covered a period of time between Aug. 5, 1947, and Feb. 28, 1950. In this interim there were 15,031 deliveries or a percentage incidence of cesarean sections of 1.9. Cesarean sections accounted for 34 per cent of the total 820 gynecological and obstetrical operative cases. The youngest patient was 15 years and the oldest was 52 years of age. Eighty-eight patients, 31 per cent, were primigravidas. One was para xix.

The indications for section were divided into 3 categories. In the first group there were 3 main classes of indications: (1) absolute indications in 18 cases including 8 with

bony pelvis contraction, 4 with irreducible placenta previa and 6 cases of vaginal or cervical tumors; (2) dangers to fetus concerned 41 cases, including 19 cases of prolonged labor, 10 of prolapsed cord in cephalic presentations, 10 of brow presentation, and 2 of postmortem cesarean section; and (3) indications threatening to life of the mother in 49 cases, including 34 cases of placenta previa centralis, 12 cases of marginal placenta previa with hemorrhage despite rupture of the membranes, 2 cases of cardiac insufficiency, and 1 of tuberculosis. The relative indications were present in 173 cases in the large Group II in the series. These included 143 cases of failure of test of labor, 10 cases of failed forceps, and 20 cases of failed version. The Group III, debatable indications were present in 2 cases, one a low-implanted placenta and one case of eclampsia.

In the failure of test of labor group, 143 patients (51 per cent of the series) were 56 in labor 2 to 6 hours, 30 in labor 6 to 12 hours, 14 in labor 12 to 18 hours; 20 in labor 24 to 36 hours; and 15 in labor more than 36 hours. In 173 sections the anesthesia of choice was spinal anesthesia with general anesthesia employed 104 times, an intravenous barbiturate Nesdonal 33 times, and local infiltration in the remaining few cases.

The technique of cesarean section was classical section in 11 cases; low cervical section in 68 cases; and modified classical and low flap operation in 203 cases. Nine of the sections were repeat operations; sterilization was performed on 7 women and cesarean hysterectomy was done on 12 patients.

The fetal mortality was 17 per cent, including 11 cases of intrauterine death, 24 cases of stillbirth, and 11 cases of neonatal death, the later deaths occurring from 1 hour to 8 days after cesarean section. There were 34 cases where the infant weighed less than 2,000 grams, 234 infants weighed between 2,000 to 3,800 grams, while 14 infants weighed more than 3,800 grams, of whom 2 infants each weighed more than 5.0 kilograms. In 35 patients operated on more than 24 hours following rupture of the membranes there were 22 living infants and among the 13 lost infants there were 7 stillbirths.

Sixty-two women had afebrile postsection clinical courses. Penicillin was used in 229 cases and sulfonamides in 141 cases. There were 12 maternal deaths, a rate of 4.2 per cent. Nine tables accompany the article. CLAIR E. FOLSOME.

Extrauterine Pregnancy

Cartoux, G., and Trân-Dinh-Dê: A Series of 301 Extrauterine Pregnancies, Gynéc. et obst. **49**: 390, 1950.

The authors report their experience with 301 consecutive cases of extrauterine pregnancies seen at the Department of Obstetrics and Gynecology at the Saigon Medical School, Thailand. These cases were seen in the interim of Aug. 5, 1947, to March 11, 1950, or a period of slightly more than 31 months, an average of at least 9 cases per month. In 1949 there were 120 cases, or approximately one ectopic pregnancy every third day during that year.

In this same interim there were 15,206 births and 1,087 abortions. The incidence of ectopic gestation was then 1.8 per cent. There were 840 gynecological and abdominal operations of which 301 were laparotomies (36 per cent) for ectopic pregnancy.

The racial distribution and incidence of ectopic pregnancy to births was observed as follows: Vietnam, 15,580 births and abortions with 283 ectopic gestations (1.8 per cent); Chinese, 556 births and abortions with 15 extrauterine pregnancies (2.7 per cent); and Cambodians, 197 births and abortions with 3 ectopic cases (1.5 per cent).

Age of the 301 patients ranged from 18 to 45 years with 65 per cent (194 cases) in the age group of 25 to 34 years. Parity distribution indicated 62 patients (21 per cent) were para 0, 76 patients (25 per cent) were para i, 58 (18 per cent) were para ii, 37 (12 per cent) were para iii, and 72 (24 per cent) had been pregnant 4 or more times. Seventy-seven per cent, 185 patients, had each had a previously normal pregnancy; 45 had had a previous abortion; while 9 gave a history of previous ectopic pregnancy. The average

time interval between the previous pregnancy and the ectopic gestation was 5 years as compared to an average of less than 3 years between normal intrauterine pregnancies.

In the 247 patients presenting a concise menstrual history it was observed that in 23 cases there had been no delay in the menstrual period; in 55 cases the menstrual period had been skipped only 1 to 15 days; the interval from the anticipated normal period ranged from 16 to 60 days in 124 cases; and more than 60 days in 45 cases.

Pain was present in 264 cases, 88 per cent, as the most constant symptom. Vaginal bleeding was observed in 187 cases, 62 per cent, and syncope or vertigo existed in 125 cases, 42 per cent. Difficulties with urination or defecation were noted in 35 cases. In 108 patients the pulse rate ranged from 10 to more than 150 beats per minute while in 89 cases the systolic blood pressure was lower than 90 mm. Hg. In 81 cases, 27 per cent, there was present muscular rigidity of the lower abdomen.

Tenderness was elicited in the pouch of Douglas 243 times, in 80 per cent of the cases. Puncture of the cul-de-sac was positive in 116 cases. Seventy-one patients were operated upon within 24 hours from admittance while the balance were operated upon 4 to 5 days following hospital admittance. Fourteen methods of anesthesia were employed. In 218 patients there was some degree of intraperitoneal hemorrhage while in 65 cases hematoceles of variable size were encountered. In two instances there was suppuration of the hematocele.

The ectopic pregnancy was localized 156 times on the left and in 124 patients it was found on the right side. The ectopic gestation was involved in the infundibular portion of the tube in 2 cases, the ampullar end in 197 cases, the isthmic area in 60 cases, the isthmo-interstitial region in 2 cases, the interstitial zone in 11 cases; it was an angular pregnancy in 7 cases, in the tubovarian area in one case, and was an abdominal pregnancy in 5 cases. In 16 cases it was not possible to localize the original site as the products of conception had been aborted into an old hematocele.

The type of operations employed to care for the ectopic pregnancy were: total unilateral salpingectomy in 140 cases; partial salpingectomy in 22 cases; salpingectomy with oophorectomy in 61 cases; salpingectomy with resection of the corresponding uterine cornu in 4 cases; simple repair of the ruptured tube in 12 cases; complete ablation of the right and left adnexa in 13 cases; simple closure of the uterine horn in 3 cases; removal of abdominal pregnancy in 5 cases; simple evacuation of a hematocele in 15 cases and evacuation of a hematocele with adnexal ablation in 26 cases. Drainage was utilized in 121 cases during the first 18 months of the study.

The coexisting complications included 2 cases of ectopic pregnancy with a coexistent intrauterine pregnancy; 2 cases with associated small ovarian cysts; in 1 case an ovarian cyst developed 2 months following removal of an ectopic pregnancy; 1 case of ectopic pregnancy terminated eventually as chorionepithelioma 2 months following the primary surgery; and 9 cases of repeated ectopic pregnancy. Postoperative sulfonamides were used in 244 cases and penicillin in 167 cases; 43 patients were completely afebrile while the remainder exhibited some type of febrile course for an average of 3 days. There were two deaths in those not operated upon, patients in extreme shock upon admission. There were 9 deaths in the operative series, or 3.0 per cent mortality rate. The article is well illustrated with 15 tables. CLAIR E. FOLSOME.

Gynecology

Haines, Magnus: Tuberculosis of the Endometrium, The Lancet 1: 436, Feb. 24, 1951.

In recent years endometrial tuberculosis has been found very commonly in England, the incidence being reported at 5 to 6 per cent in groups of women studied because of infertility. Histologically, tuberculous lesions of the endometrium resemble those elsewhere in the body, but periodic shedding of the endometrium usually prevents formation of the mature tubercle and other advanced stages. Essentially, the endometrial lesion is one with a central zone of endothelioid cells with eosinophilic cytoplasm, surrounded by

lymphocytes and plasma cells. There may be only an infiltration of inflammatory cells in the stroma, and, if no other cause for inflammation is found, it is wise to suspect tuberculosis.

Diagnosis is best established by endometrial biopsy, with microscopic and culture (guinea pig and direct) studies on the endometrium. The disease is hematogenous, although tubal tuberculosis may coexist. Frequent biopsies are inadvisable. The author advises treatment with 1.0 Gm. of streptomycin and 10 grains of p-aminosalicylic acid daily for three months. Apparent cures should not be accepted until there has been clinical cure with negative biopsies (taken every four to six months) for two years.

IRVING L. FRANK.

Borras, Pablo E.: Diffuse Papillomatosis of the Vagina, Ginecologia **6**: 11, 1951.

The author, from Rosario, Argentina, describes a case of diffuse papillomatosis of the vagina in a 50-year-old patient. He treated these benign lesions with an indwelling radium application and they disappeared completely. CLAIR E. FOLSOME.

Vokaer, R.: Histological, Histometric and Histophotometric Observations of the Human Endometrium, Gynéc. et obst. **50**: 372, 1951.

The author, from Brussels, reminds us of the importance of nucleic acids in cytological studies. There is a relative constancy of the quantity of desoxyribosenucleic acid in all cells present in endometrium taken at any specific period of time in the cycle.

He utilizes the method of Lison in his histophotometric studies of the endometrium which demonstrates variable values of nucleic acid in the mitotic phases taken at different times from endometrial specimens. He observes that the estrogenic activity releases a considerable increase in the nucleic acids while the progesterone activity decreases these values. He illustrates his findings by studying multiple specimens of endometrium taken frequently, at different days of the cycle, from a single case over a period of three menstrual periods. Fourteen figures and photomicrographs accompany the article.

CLAIR E. FOLSOME.

Briney, Allan K., and Hodes, Philip J.: Urinary Incontinence in Women: Roentgen Manifestations, Radiology **58**: 109, 1952.

This paper confirms the original observations of Muellner, namely, that when bladders are rendered opaque either by the intravenous injection of dye or the insertion of radiopaque material into the bladder, the normal bladder has a smooth layer outline until just prior to voiding, when a small teatlike projection occurs at its lowermost portion. However, in women with stress incontinence the small teatlike projection is present at all times. L. M. HELLMAN.

Gynecologic Operations

D'Ingianni, Vincente, and Fontenelle, I. L.: Implantation of the Salpinx Employing a Cannula, South. M. J. **44**: 1139, 1951.

Surgical procedures designed to establish patency in the occluded Fallopian tube have been almost universally disappointing. Greenhill analyzed 818 such procedures in which 54 pregnancies resulted, or one pregnancy for every 15 operations. The authors describe an operation which they believe carries a more favorable prognosis.

This procedure includes a resection of the occluded portion of the tube and implantation into the uterus using a steel cannula to safeguard maintenance of the lumen. A transverse suprapubic incision is made and the salpinx presenting the least disease is selected for implantation. A circular incision is made through the tube distal to the occlusion and then a longitudinal incision 2 mm. in length is made in the proximal end of the patent portion of the tube. Three triple 0 chromic sutures are placed in the endo-

salpinx, the sutures are tied and held in double lengths. An incision is made into the posterior wall of the uterus entering the uterine cavity. A steel wire with its distal end bent on itself is passed into the uterine cavity and through the cervical os into the vagina. There is an eye in the end of the cannula protruding from the uterine incision into which a suture is threaded which passes through the lumen of the tube and acts as a guide and traction line to guide the tube over the cannula. Next the sutures attached to the proximal end of the tube are passed through the uterine incision and into the uterine cavity, passing out from the cavity to the serosal surface of the uterus and when tension is made upon these three sutures, the tube is pulled into the uterine cavity over the cannula. The cannula is left in place from three to four months.

The authors report that in 16 patients who had an implantation according to this technique, five have become pregnant and two of these are in their second pregnancy.

WILLIAM BICKERS.

White, Margaret Moore: Four Cases of Re-implantation of the Fallopian Tubes, J. Obst. & Gynaec. Brit. Emp. **58**: 381, 1951.

The author gives the technique, the case histories, and the final outcome of reimplantation of the Fallopian tubes for the relief of sterility in four personal cases. Six of the eight tubes reimplanted were demonstrated to be patent by the Rubin test ten days postoperatively. Two patients became pregnant; one carried to full term, the other had a tubal pregnancy. The preoperative diagnosis of the exact location of the tubal obstruction is most important. The technique of the operation must be meticulous and the Rubin test should be performed on the tenth postoperative day.

HARVEY B. MATTHEWS.

Labor, Management, Complications

Seitz, Ludwig: The Etiology of the Onset of Labor After Fetal Death in the Last Trimester of Pregnancy, Geburtsh. u. Frauenh. 11: 577, 1951.

It is not rare that fetal death occurs during the third trimester of pregnancy without the expulsion of the products of conception for days or even weeks after such death is present. In general when this occurs delivery does not supervene until the fetus is more or less macerated. Intrauterine death and delayed labor are independent phenomena and are not interrelated in any manner. In determination of the level of the estrogenic hormone and progesterone changes in the maternal blood, according to the views of the author, no variations are noted when the fetus is dead or when it is alive. However, after the fetus dies, the placenta and the baby no longer have an active blood circulation. It is because of this that a ferment action occurs which results in a change in the molecular consistency in the muscle cells of the uterus. It is because of this change that labor is induced and the fetus is expelled. The rate of these changes and the building up of these end products is inversely proportional to the time that the baby is retained in the uterus.

L. B. WINKELSTEIN.

Hanley, Bernard J.: Amniotomy for the Elective Induction of Labor at or Near Term, West. J. Surg. **59**: 262, 1951.

The first recorded induction of labor was done in 1738 in England when a midwife, Mary Donnelly, ruptured the membranes in a patient with a contracted pelvis. During the last two decades the procedure has gained in favor especially in America but dissenting voices such as those of Kosmak and Irving are occasionally heard. Elective induction of labor has been and will continue to be a subject of discussion for the years to come. In this paper the author reports his experience over a period of ten years with the induction of labor at or near term by amniotomy done solely for elective reasons. There were

653 cases representing private patients delivered during the period Jan. 1, 1940, to June 30, 1950. This represents approximately 10 per cent of all obstetrical cases managed by the author during this period.

The criteria used for determining the patient's eligibility for induction were: (1) cephalic presentation at the ischial spine; (2) a cervix 50 per cent effaced, soft, and dilated to 1 cm.; (3) a pelvis through which it could reasonably be assumed normal delivery would occur. The membranes were stripped thoroughly from the lower uterine segment and then ruptured with a Wilson amnion point. There were no maternal mortalities in this group and maternal and fetal morbidity compared favorably with that of patients who started labor spontaneously. The gross fetal mortality was 1.2 per cent and if those babies born with defects incompatible with life were excluded a corrected fetal mortality of 0.5 per cent is attained. Cord prolapse did not occur. The average length of labor in the induced-labor group was much shorter than that in the patients who went into labor spontaneously. There was no apparent anatomical injury sustained by the soft tissues in those patients who were delivered following amniotomy.

The author attempts to answer the criticisms which are commonly leveled at this procedure. He emphasizes that the sole moral and legal responsibility of elective induction of labor rests upon the shoulders of the operator. "Are we justified in initiating a condition which always occurs spontaneously?" he asks. Elective induction of labor does not increase the incidence of dystocia or obstetrical emergencies if the prerequisites for the procedure are fulfilled. Moreover, the obstetrician by amniotomy elects the time and place of parturition. The sad paradox of obstetrics, he says, is that the obstetrician is often called upon to exercise his best judgment and demonstrate his greatest skill when his physical resources are at their lowest ebb. He emphasizes that labor is no longer or harder when electively induced and patients having once delivered by this method welcome amniotomy in succeeding deliveries.

Interesting discussion followed in the wake of this paper which was in general favorable to the procedure. There was one discusser, however, who favored medical over a surgical induction. WILLIAM BICKERS.

Dexeus Trias de Bes, J. M.: Modification of the Kielland Forceps to Facilitate Direct Application of the Anterior Blade, Toko-ginec. práct. **92**: 276, 1951.

The author postulates that direct application of the anterior Kielland Blade, as described by Lorenzetti, to the transverse fetal head is more logical, simpler, and safer than the inversion method of Kielland, and easier than the wandering method of application.

In order to insert the anterior blade directly in the narrow space between the anterior parietal and the symphysis, it is necessary to begin the maneuver with the forceps handle perpendicular to the floor, and gradually elevate it as the blade progresses inward. However, the initial vertical position of the handle is often impeded by the edge of the table or by the shank of the forceps striking the perineum. If, because of these obstacles, the handle is not lowered sufficiently, the toe of the blade will be at an angle to the parietal and cannot easily glide into the narrow tunnel where it must enter, unless the fetal head is small and extra space available.

Some obstetricians overcome the table obstacle by placing the patient in lateral decubitus while the anterior blade is being inserted. This, however, does not dispose of the perineal obstacle.

The author has devised a modification of the Kielland forceps consisting of an articulation of each blade 14 cm. from the toe. This permits the handle and shank to be flexed away from the edge of the table and perineum without changing the orientation of the blade. A screw lock, with separate key, immobilizes the hinge in normal position. Since the articulation does not affect the shape of the instrument, it remains a Kielland forceps which can be used in the classical Kielland manner if desired.

For direct application of the anterior blade, the handle is flexed outward at the hinge so that it is parallel to the floor while the blade is slipped over the anterior parietal.

The hinge is then locked in normal position. According to the author, direct application of the anterior blade is very simple with the modified instrument. The posterior blade is inserted in the usual manner without using the hinge.

This forceps has no similarity to the Barton forceps either in shape or purpose.

MAGIN SAGARRA.

Latiers, F.: Labor in Elderly Primiparas, Bull. Assoc. de gynéc. et obst. de lang. franç. **1:** 550, 1949.

Among 4,504 deliveries at the Obstetrical and Gynecological Clinic at Strasbourg during the three-year period, 1946 to 1948, inclusive, the author surveys the labor histories of 332 cases, 7.37 per cent, of elderly primiparous patients more than 30 years of age. The age distribution included 186 patients, aged 30 to 34 years, 4.12 per cent, and 146 women, aged 35 to 45 years, 3.24 per cent.

Toxemia of pregnancy was found in 22 cases, 6.62 per cent, and premature labor in 9.03 per cent of the series. Nearly three-fourths of the primiparas over 35 years, 75.14 per cent, and approximately two-thirds of the primiparas of 30 to 34 years of age, 68.41 per cent, had a duration of labor of less than 12 hours, while 2.12 per cent and 1.36 per cent of the two age groups were in labor more than 24 hours.

In 77 cases, 23.19 per cent, of the series there was premature rupture of the membranes. Anomalous presentations were encountered in 3.76 per cent of women aged 35 to 45 years and in 5.47 per cent of women aged 30 to 34 years. Operative obstetrical care was required in 13.97 per cent of the women aged 35 to 45 years and in 21.33 per cent of those 30 to 34 years. The oldest age group required forceps intervention 5.37 per cent of the time while the next elderly group required forceps in 6.84 per cent of the cases. The average incidence in women under 30 years of age was 1.13 per cent. Cesarean section was done in 5.91 per cent (aged 35 to 45 years) and 12.32 per cent (aged 30 to 34 years). The average infant mortality was 3.21 per cent in women less than 30 years of age as compared to 6.45 per cent in those aged 35 to 45 years, and 7.53 per cent, aged 30 to 34 years.

CLAIR E. FOLSOME.

Menopause

Chiara, Antonio: A Reinterpretation of the Pathogenesis and Therapy in Menopausal Hypertension. A Clinical Study, Ann. ostet. e ginec. **73:** 583, 1951.

The author re-examines the many theories and hypotheses anent the development of menopausal hypertension. He classifies this entity as primarily one resultant from attempts of the body to adapt itself to altered metabolic and endocrine states of imbalance, hence he terms menopausal hypertension a disease of adaptation. In his extensive review he re-evaluates the numerous endocrine and vasomotor theories of pathogenesis. In his opinion the most reliable theory is the so-called neurohormonal theory. He stresses the state of endocrine imbalances affecting small blood vessel innervation. The author then reports in detail his management of 8 patients exhibiting a climateric hypertension. In his therapy he utilized progesterone, with or without ascorbic acid, by intramuscular and/or intravenous injections. The progesterone dosage varied from 10 to 25 mg. and the ascorbic acid in doses up to 1.0 Gm. In his opinion this group of patients gave excellent response both in a decrease in the vasomotor and hypertensive symptomatology and in clinical findings. He concludes progesterone is of particular value in such cases since it tends to restore endocrine equilibrium and hence diminish imbalanced response upon the capillaries and arterioles. Eight figures accompany the article.

CLAIR E. FOLSOME.

Menstruation, Dysmenorrhea

Sharman, Albert: Menstruation After Childbirth, J. Obst. & Gynaec. Brit. Emp. **58:** 440, 1951.

The reappearance of menstruation after childbirth has long been under investigation but no detailed analysis as to the date of onset, influence of lactation, or subsequent rhythm

is available. This present study was undertaken to endeavor to bring order out of chaos. For this purpose the author has analyzed from every conceivable angle the data on 834 women from date of delivery to nine months later. Four hundred and twenty-six were primiparas and 408 multiparas. Table I tabulates parity in relation to lactation. Table II gives age distribution in relation to lactation. Table III details the re-establishment of menstruation in both primiparas and multiparas in relation to (a) lactating, (b) partly lactating, and (c) nonlactating mothers. Re-establishment of menses between 12 and 36 weeks post partum occurred in 67 per cent lactating, 26 per cent partly lactating, and 9 per cent of nonlactating mothers. Table IV has to do with regularity of menstruation as related to lactation. Here it is seen that 72.5 per cent of lactating women had regular periods; 92.6 per cent of those partly lactating had regular periods; while 90.2 per cent of the nonlactating had regular periods. Age, parity, the presence or absence of lactation always influence menstruation—time of onset and rhythm—following childbirth. Last, it is interesting to note that of these 834 obstetric patients, 196, or 23.5 per cent, were lactating; 356, or 42.7 per cent, were partly lactating; and 282, or 33.8 per cent; were nonlactating. HARVEY B. MATTHEWS.

Miscellaneous

Confalonieri, C., and Montorsi, S.: The Activity of Androstendiol Upon the Uteri of Castrated Female Rabbits, Minerva ginec. 3: 656, December, 1951.

The authors, reporting from the Pharmacology Institute of the University of Milan, studied the behavior of uterine strips of castrated female rabbits, after pretreatment with androstendiol. The uterine strips of animals treated previously with high doses of androstendiol (dosage ranged daily from 250 to 2,000 gammas) showed a reaction to various drugs (Adrenalin, noradrenalin, acetylcholine, histamine, and posterior pituitary substance) in a similar manner as the uterine strips of animals previously treated with small doses of estrogens.

Six photographs of the kymographic tracings illustrate well the authors conclusions.

Döring, Gerd, and Schaefer, Edith: Further Studies on the Effect of Progesterone on Body Temperature, Med. Klin. 47: 148, 1952.

Rhythmic changes of body temperature were known, for a long time, to occur with changes in the menstrual cycle. Similar changes in temperature also occur during pregnancy. Basically, there is a rise in basal body temperature, averaging 0.5° C. to 1.0° C. at or around the time of ovulation, and remaining elevated until just before menstruation occurs. If pregnancy supervenes, the premenstrual decline is not noted, and the temperature remains elevated throughout the entire period of gestation. The cause of this elevation has long been debated and has been ascribed to many different hormonal changes. The prevalent theory is that the secretion of progesterone exerts this influence upon the basal thermodynamic changes. The authors felt that further experimental investigation was necessary. They studied the basal temperature curves in ten normal nonpregnant women between the ages of 19 and 30 years. After having established a graph of the temperature changes, they gave 50 mg. of progesterone in oil intramuscularly, on the eighth day of the cycle. The eighth day was considered best since the menstrual flow had stopped in all and ovulation had not yet occurred. Increases in the basal body temperature were noted in all cases, and varied from 0.25° C. to 0.5° C., with an average of 0.34° C. These increases all occurred within 24 hours of the injection and persisted for approximately 24 hours. Although the increases were small, they were noted consistently. The authors have concluded, therefore, that the thermogenetic effect is due to increased amounts of circulating corpus luteum hormone in the body, since on introduction of this hormone a temporary increase in basal temperature is noted.

L. B. WINKELSTEIN.

Newborn

Hegnauer, Hermann: The Frequency of Fetal Deformities When Compared to the Mother's Age at the Time of Pregnancy, Geburtsh. u. Frauenh. 11: 777, 1951.

In a study of 140,000 deliveries, the relationship between the frequency of fetal anomalies and deformities was investigated in relation to the age of the mother at the time that the pregnancy occurred. It was noted that women between the ages of 36 and 40 years gave birth to twice as many malformed infants as did the women of younger ages. Furthermore, in the cases of the women above the age of 40 years, the incidence was over three times as great. The only relationship between fetal maldevelopment that could be definitely established was with the age of the mother and had no bearing on parity as the incidence of malformations was almost identical in primiparas as in multiparas. In a general survey of the entire group this relationship was definitely established concerning the absence of limbs, the presence of hairlip, or of genitourinary maldevelopment. It was further noted that as the age of the mother increased, especially above 40, the incidence of abnormalities of the central nervous system, the presence of anencephalus, hydrocephalus, mongolism, and hydramnios increased. This was remarkable in view of the fact that in no instance in this general age group were difficulties of the spinal cord present. Congenital hernia, on the other hand, was many more times frequent in older women's offspring as compared with the children of younger mothers. The authors conclude that since these anomalies, in general, increase in percentage as the age of the mother increases and since no other causable factors could be demonstrated, the probable reason is some undiagnosable damage to the germ cell by the continuance of a static state for many years in the ovary.

L. B. WINKELSTEIN.

Tregillus, John: The Asphyxial Membrane in the Lungs of Liveborn Infants, J. Obst. & Gynaec. Brit. Emp. 58: 406, 1951.

In his introduction the author states, "in the course of postmortem examinations on 244 newborn infants an eosinophilic hyaline membrane which lined bronchioles, alveolar ducts and alveoli was found in the lungs of 35 liveborn infants." The clinical and pathological findings in these 35 liveborn infants whose lungs showed the characteristic asphyxial membrane are given in detail. Various theories as to the etiology of this lesion are discussed and the author's ideas as to its origin are given. Three photomicrographs illustrate the pathology found. The author's conclusions are as follows:

1. The asphyxial membrane (hyaline membrane) found in the lungs of liveborn infants is formed by necrosis and hyalinization of bronchiolar epithelium. It is suggested that this lesion is due to anoxia and that its higher incidence in immature infants is due to the incomplete development of their lungs.

2. The formation of an asphyxial membrane increases the degree of anoxia and thus a vicious cycle is established.

3. All immature infants of a birth weight of 1,920 Gm. (4 pounds) or less and any infant born in shock or with cyanosis should be given continuous oxygen for the first few days of life. This enhances the likelihood of fully expanding the lungs.

HARVEY B. MATTHEWS.

Pregnancy, Complications

Marmey, J., and Lacroix, A.: Recklinghausen's Disease and Pregnancy; Cesarean Section for Vaginal Neurofibromatosis, Féd. Soc. de gynéc. et obst. de lang. franc. 3: 645, 1951.

The authors report a case of von Recklinghausen's disease complicating pregnancy. The primiparous patient exhibited the classical findings of this complication having multiple neurofibromas over the back, the perineum, and in the vagina and on the vulva. There was present a coexisting toxemia, blood pressure 160/120 with a proteinuria. Cesarean section under spinal anesthesia was done with ease and a 2,550 gram living infant delivered. Biopsies of several of the vulval and vaginal lesions revealed typical neurofibromas.

Dailey, Morris E., and Benson, Ralph C.: Hyperthyroidism in Pregnancy, Surg., Gynec. & Obst. **94**: 103, 1951.

This is a timely article which presents 21 cases of hyperthyroidism occurring in 11,390 pregnancies and contains a summary of recent literature on this subject. The authors feel that hyperthyroidism has no effect on the well-established pregnancy although there is some evidence that early pregnancy is more liable to abortion. There is no increase in the incidence of toxemia or postpartum hemorrhage.

Pregnancy appears to be a significant factor in the initiation, or at least the time of onset, of hyperthyroidism. However, it does not appreciably affect the course of the disease. There is no increase in fetal abnormalities. The authors recommend subtotal thyroidectomy preceded by adequate medical preparation including iodine but without the use of thiouracil. The objection stated to thiouracil is that it crosses the placenta freely and may interfere with the fetal thyroid. L. M. HELLMAN.

Kistner, Robert W., Hertig, Arthur T., and Reid, Duncan E.: Simultaneously Occurring Placenta Previa and Placenta Accreta, Surg., Gynec. & Obst. **94**: 141, 1952.

This paper calls attention to a rare but singularly important complication of placenta previa. Accreta complicating previa has been described in the literature only 21 times prior to 1950. The authors reviewed the recorded cases together with 9 which occurred at the Boston Lying-in Hospital during the past 15 years. They suggest that packing of the lower segment or the use of sutures in the lower segment is to no avail. They advocate the use of supravaginal hysterectomy with figure of eight sutures placed in the cervical stump. There was one maternal death in their series. L. M. HELLMAN.

Toxemia

Mukherjee, Chunilal: Hepatic Function Tests in Toxemias of Pregnancy—Thymol Turbidity Test, J. Obst. & Gynaec. India **2**: 5, Sept., 1951.

The thymol turbidity test has been used as a test for hepatic damage. It does not test any known function of the liver and should be regarded as an indication of disturbed liver metabolism.

In normal pregnancy it was shown, in a study of 72 patients, that the thymol turbidity test was not changed significantly from that in normal nonpregnant women. In the toxemias of pregnancy turbidity is found to increase when compared with that in normal gestation. Abnormal values are obtained in cases of toxemia, however, only when the disease is of long duration and great severity. The incidence of positive results is higher in eclampsia than in pre-eclampsia. The results obtained from this test indicate that there may be gross hepatic damage and that there is a progressive decrease in the functional reserve of the liver. Such widespread and serious damage to the function of the liver necessarily connotes systemic disease of a grave type.

The incidence of a positive test in a series of patients with eclampsia was 39.0 per cent. When the test is taken during the stage of convulsion and coma the positive result increases to 71.5 per cent. In the patients with pre-eclampsia of a severe type a positive test is obtained in 5.6 per cent. WILLIAM BICKERS.

Aguero, Oscar: Pre-eclampsia and Eclampsia, Rev. obst. y ginec., Caracas **11**: 437, 1951.

The author details the three current theories concerning the etiology of toxemia of pregnancy: (1) the placental theory; (2) the Smiths' theory; (3) the ACTH theory.

The placental theory has two interpretations: (a) presupposes the existence of an increased number of placental infarctions in toxemic patients, with entrance into the circulation of toxic substances produced in the infarcted areas. Chief objection to this theory is

that placental infarctions are commonly found in normal pregnancies, and that their number and size are no different in toxemic and nontoxemic mothers: (b) invokes uterine ischemia, which permits the formation of a "toxin" in the placenta; this "toxin," which has not been identified as yet, would enter the circulation and produce the pathologic changes found in eclampsia in the kidneys, liver, and brain.

The Smiths' theory, propounded by O. W. and G. V. Smith, is an endocrine theory, based on their hormonal studies in normal and toxemic patients. The two principal findings are: (a) an increase in circulating gonadotrophin, and (b) a decrease in the blood level of estrogen and progesterone before and during toxemia. The Smiths believe that these findings indicate premature senility of the placenta due to premature hormonal deprivation and, as a consequence, the appearance of a circulating "toxin," the action of which is similar to that of the "menstrual toxin" which they have found in menstrual blood.

The ACTH theory, the most recent one, postulates that in toxemia there is an increase in production of ACTH by the pituitary gland, and that the resulting excessive amount of circulating ACTH would explain the pathological visceral changes found in toxemia. The basis of this theory is the "syndrome of adaptation" propounded by Selye.

The author reviews the present-day treatment of pre-eclampsia and eclampsia. He suggests that medical conservative management of pre-eclampsia should not extend beyond 15 to 22 days in the absence of evident improvement. MAGIN SAGARRA.

Berlin, Nathaniel I., Hyde, Grace M., Lawrence, John H., Parsons, Robert J., and Port, Shirley: The Blood Volume in Pre-eclampsia as Determined With P^{32} Labeled Red Blood Cells, Surg., Gynec. & Obst. **94:** 21, 1951.

The authors determined the blood volume, the plasma volume, and total red cell volume in 8 patients with pre-eclampsia using P^{32} labeled red cells. There was a reduction in blood volume of 18.9 c.c. per kilogram (26 per cent), in total red cell volume of 4 c.c. per kilogram (16 per cent) and in plasma volume a reduction of 14.7 c.c. per kilogram (31 per cent). Forty-seven women in the third trimester of pregnancy were used as controls for this study. L. M. HELLMAN.

Radiation

Kepp, R. K.: Improved Technique for Deep X-ray Therapy in Advanced Cases of Carcinoma of the Cervix, Geburtsh. u. Frauenh. **11:** 771, 1951.

Treatment of metastases of carcinoma of the cervix is difficult and sometimes impossible. In general it has been thought that the use of deep x-ray therapy was often unfavorable and definitely dangerous, and it had been discarded almost entirely in many of the continental clinics. However, in 1950 the American Congress on Obstetrics and Gynecology advocated the use of deep therapy and reported generalized beneficial results. A great deal of the effect of deep radiation is dependent upon the methods of administration and the amount of x-radiation given. The ideal method of therapy must include maximal doses to the original lesion as well as to the carcinomatous mestastases and also must include maximal protection of all other normal tissues. This applies not only to the irradiation of x-ray but also to that of radium (mesothorium) emanation. The author feels that with radium alone a primary cervical carcinoma can be treated and cured without any difficulty whatsoever, but that deep-seated metastases cannot be reached. He feels also that radium needles and other radium applicators into the parametrium are worthless and produce large percentages of fistulas, necrosis, hemorrhage, and bladder and colon pathology. Cross x-radiation is similarly felt to to be without value. In the evaluation of radical surgery including lymph gland dissection of the pelvis the author feels here too that there is not too great hope for a cure. Therefore he feels that all methods of therapy have disadvantages which up to now have not been overcome.

According to the view of the writer, radium, when properly administered, gives the best chance for cure of the primary lesion. In laying down rules for general treatment, stress must be placed not only on the treatment of the primary carcinoma of the cervix but also on treatment of the parametrial metastases which are felt to be always present. The author describes a new type of x-ray tube where the anode is so constructed that it can be introduced into the vagina and, with special angular gynecological cones, can be directed in such a manner as to reach the parametrium as far out as the lateral pelvic wall without too much damage to healthy adjacent tissue. This tube is pictured and described in such a manner that by means of direction against the lateral vaginal wall and the angulation of the tube toward the lateral pelvic wall, the dosage of x-ray is directed primarily toward the parametrium. This tube was previously described by Witte in 1929 and used in the author's clinic since.

Treatment of the primary carcinoma of the cervix is accomplished by means of intracervical radium tubes. For the treatment of lateral metastases and lymph nodes, x-ray therapy according to the outlined technique was followed which was combined with further radium application. Five-year cures were noted as follows: Group I—operation alone, 48.6 per cent cured as compared with 68 per cent cured by means of operation and radiation; Group II—x-ray alone, 47 per cent cured; Group III—36 per cent cured; Group IV—0 per cent cured.

Due to the limited field of the new x-ray tube, the rays may be localized so that the amount of x-radiation can be safely increased. However, care must still be taken to avoid the production of bladder and rectal pathology. With the method described results are much better than with more generalized radiation, and although fistulas did occur the frequency was much less. In summary the author feels that with multiple pelvic metastases, the use of x-ray has value and compares favorably with the more radical evisceration procedures practiced by Brunschwig.

L. B. WINKELSTEIN.

Sterility

Pollock, Mary, and Preiskel, Ella: Hysterosalpingography With a Water-soluble Medium in the Investigation of Infertility, J. Obst. & Gyanec. Brit. Emp. 58: 421, 1951.

This paper has to do with the study of 310 infertile women patients who were examined by a simple technique of hysterosalpingography using a water-soluble contrast medium (Pyelosil [Glaxo] 35 per cent). The advantages of this medium over Lipiodol and viscous diodone preparations are given in detail. These latter preparations are "heavy," do not show as fine detail, and are more likely to produce complications (embolus, infiltration into tissues, etc.). The aqueous diodone solution (35 per cent) fulfills all radiographic requirements and has very few of the disadvantages of the viscid agents. However, one distinct disadvantage must be mentioned, viz., it is more irritating to the pelvic peritoneum than Lipiodol. The author's conclusions may be noted as follows: (1) All cases of female sterility without obvious cause should be subjected to hysterosalpingography if pregnancy does not occur within a reasonable time. (2) A watery solution of 35 per cent diodone is the most satisfactory contrast medium available at the present time. (3) A comparison is given between the findings after the insufflation and hysterosalpingography. (4) The disadvantages and incidence of complications of this technique are noted.

HARVEY B. MATTHEWS.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* William P. Healy, New York. *Secretary,* John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Next meeting, Lake Placid Club, May 13, 14, and 15, 1953.

American Association of Obtetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* Leroy A. Calkins, Kansas City, Kan. *Secretary,* William F. Mengert, 2211 Oak Lawn Ave., Dallas 4, Texas. Annual meeting Hot Springs, Va., September 11, 12, and 13, 1952.

Central Association of Obstetricians and Gynecologists. (1929) *President,* John I. Brewer, Chicago, Ill. *Secretary-Treasurer,* Harold L. Gainey, 116 S. Michigan Ave., Chicago 3, Ill. Annual meeting, Memphis, Tenn., Oct. 30-Nov. 1, 1952.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* F. Bayard Carter, Durham, N. C. *Secretary-Treasurer,* John C. Burwell, Jr., 416 Jefferson Bldg., Greensboro, N. C. Next meeting, Havana, Cuba, Jan. 29–Feb. 2, 1953.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Arthur B. Hunt, Rochester, Minn. *Secretary,* Bernard J. Hanley, 1930 Wilshire Blvd., Los Angeles, Calif. Annual meeting, Chicago, Ill., June 9-13, 1952.

New York Obstetrical Society. (1863) *President,* S. A. Cosgrove. *Secretary,* Charles M. McLane, 960 Park Ave., New York 28, N. Y. Second Tuesday, from October to May.

Obstetrical Society of Philadelphia. (1868) *President,* J. Marsh Alesbury. *Secretary,* Paul O. Klingensmith, 133 S. 36th St., Philadelphia 4, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* M. Edward Davis. *Secretary,* Edwin J. De Costa, 720 S. Michigan Ave., Chicago 3, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Stanley C. Hall. *Secretary,* Leslie Hughes Tisdall, 615 Third St., Brooklyn 15, N. Y. Third Wednesday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

The Obstetrical and Gynecological Society of Maryland. (1929) *President,* Emil Novak. *Secretary-Treasurer,* W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Joseph G. Crotty. *Secretary,* Robert R. Pierce, 116 William Howard Taft Road, Cincinnati 19, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* J. B. Marshall. *Secretary,* David E. Booker, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. President, William Sharkey. *Secretary-Treasurer,* Jack W. Dowsett, 1020 S. W. Taylor St., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* A. C. Williamson. *Secretary-Treasurer,* William Gibson, 1010 Center St., Pittsburgh 21, Pa. Meetings, first Monday of each month, October to May.

Obstetrical Society of Boston. (1861) *President,* George W. Waterman. *Secretary,* A. Gordon Gauld, 1180 Beacon Street, Brookline 46, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Roy E. Fallas, Los Angeles, Calif. *Secretary-Treasurer,* Donald G. Tollefson, 511 South Bonnie Brae St., Los Angeles 5, Calif.

Washington Gynecological Society. (1933) *President,* J. Bay Jacobs. *Secretary,* Allan E. King, 915 19 Street, N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Harry Meyer. *Secretary,* Abe Golden, 1430 Tulane Ave., New Orleans 12, La. Meetings held October, November, January, March, and May.

St. Louis Gynecological Society. (1924) *President,* Paul Fletcher. *Secretary,* J. Russell Vaughan, 634 North Grand Blvd., St. Louis 3, Mo., Regular meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Chester L. Cooley. *Secretary,* Edmund F. Anderson, 2445 Ocean Ave., San Francisco 27, Calif. Regular meetings held second Friday in month from October to April, Sir Francis Drake Hotel, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* S. Foster Moore. *Secretary-Treasurer,* Carey Hiett, 603 College Avenue, Fort Worth 4, Texas.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* O. W. Picard. *Secretary,* Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Nathan N. Cohen. *Secretary,* Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. (1940) *President,* W. N. Jones. *Secretary,* Herbert H. Thomas, 1005 South Twenty-first Street, Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Gerald Thomas. *Secretary-Treasurer,* Hugh Nuckols, Seattle, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.

Denver Gynecological and Obstetrical Society. (1942) *President,* Edward L. Harvey. *Secretary-Treasurer,* Jack M. Simmons, Jr., 804 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Fred J. Hofmeister. *Secretary-Treasurer,* Alice D. Watts, 324 East Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* Jesse A. Rust, Jr. *Secretary-Treasurer,* Ralph L. Hoffman, 2111 Fifth Ave., San Diego 1, Calif. Meetings held on the last Friday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Robert B. Woodhull, Minot, N. D. *Secretary-Treasurer,* John S. Gillam, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Henry C. Spalding. *Secretary,* Chester D. Bradley, 2914 West Avenue, Newport News, Va. Meetings held in April and October.

Columbus Obstetric-Gynecologic Society. (1944) *President,* Allan C. Barnes. *Secretary,* Leonard B. Greentree, 350 East Broad St., Columbus, Ohio. Meetings held last Wednesday of each month from September to May.

Naussau Obstetrical Society. (1944) *President,* Robert S. Millen. *Secretary-Treasurer,* Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Benjamin Karen. *Secretary.* Alex Charlton, 1749 Grand Concourse, New York 53, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* C. W. Knudson. *Secretary-Treasurer,* L. Bruce Donaldson, 805 Medical and Dental Bldg, Seattle 1, Wash. Meetings held in spring and fall. Next meeting to be held in Seattle, Oct. 11, 1952.

Kansas City Gynecological Society. (1922) *President,* Kenneth E. Cox. *Secretary,* James E. Keeler, 4301 Main St., Kansas City, Mo. Meetings last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* E. W. Cartwright. *Secretary-Treasurer,* A. N. Webb, 3130 W. 6th St., Los Angeles 5, Calif. Meetings, second Tuesday of September, November, January, March, and May.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* F. Bayard Carter. *Secretary,* Richard L. Pearse, 604 W. Chapel Hill St., Durham, N. C. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* A. B. Nash. *Secretary,* G. A. Simpson, Royal Victoria Hospital, Montreal, Quebec. Annual meeting, Banff, Alberta, June 6-8, 1952.

Akron Obstetrical and Gynecological Society. (1946) *President,* Donald C. Snyder. *Secretary-Treasurer,* Robert M. DeWitt. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio Bldg.

Minnesota Obstetrical and Gynecological Society. *President,* William F. Mercil. *Secretary-Treasurer,* Rodney F. Sturley, 350 Saint Peter St., St. Paul, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* John D. Milton. *Secretary,* Richard F. Stover, 701 duPont Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Ralph Luikhart. *Secretary-Treasurer,* Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* John W. Records. *Secretary-Treasurer,* Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.

Cleveland Obstetrical and Gynecological Society. (1947) *President,* J. L. Reycraft. *Secretary,* G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Robert A. Mackenzie. *Secretary,* Felix H. Vann, 242 Engle St., Englewood, N. J. Meetings semiannually.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Herbert E. Bowles. *Secretary,* James T. S. Wong, 1415 Kalakaua Ave., Honolulu, T. H. Meetings third Monday of each month, Mabel Smyth Building.

Oregon Society of Obstetricians and Gynecologists. *President,* James M. Whitely. *Secretary-Treasurer,* William O. Thomas, Jr., 1735 N. Wheeler Ave., Portland 12, Ore. Meetings held on third Friday of each month from October to May.

National Federation of Obstetric-Gynecologic Societies. (1945) *President,* Ralph E. Campbell. *Secretary,* Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.

Dayton Obstetrical and Gynecological Society. (1937) *President,* C. E. Mumma. *Secretary,* N. J. Thompson, 610 Harries Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President,* W. P. Devereux. *Secretary,* Oran V. Prejean, 4317 Oak Lawn Ave., Dallas, Texas. Meetings in spring and fall.

Queens Gynecological Society. (1948) *President,* James, V. Rizzi. *Secretary,* George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.

Mississippi Obstetrical and Gynecological Society. (1947) *President,* William B. Wiener, Jackson, Miss. *Secretary-Treasurer,* J. A. K. Birchett, The Street Clinic, Vicksburg, Miss. Meetings held semiannually.

Florida Obstetric and Gynecologic Society. (1948) *President,* Robert G. Spicer. *Secretary-Treasurer,* Dorothy D. Brame, 1235 Kuhl Ave., Orlando, Fla. Next annual meeting, April, 1951, at Hollywood, Fla.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* John M. Fleming. *Secretary-Treasurer,* Frank B. C. Geibel, 1517 Hampton St., Columbia 1, S. C. Meetings held in spring and fall.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* Milton G. Potter. *Secretary,* Harry G. LaForge, 957 Delaware Ave., Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.

El Paso Gynecological Society. (1948) *President,* C. C. Boehler. *Secretary-Treasurer,* Robert J. Cardwell, 414 Banner Bldg., El Paso, Texas.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* Clyde Sparks, Ashland, Ky. *Secretary-Treasurer,* J. B. Marshall, Louisville, Ky.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* Gerald W. Gustafson. *Secretary-Treasurer,* C. O. McCormick, Jr., 621 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.

Houston Obstetrical and Gynecological Society. (1939) *President,* E. A. Chandler. *Secretary-Treasurer,* J. T. Armstrong, Hermann Professional Bldg., Houston 5, Texas. Meetings held first Tuesday of each month except July, August, and September.

Iowa Obstetric and Gynecologic Society. *President,* J. H. Randall. *Secretary,* William C. Keettel, Iowa City, Iowa.

Memphis Obstetrical and Gynecological Society. (1950) *President,* Frank E. Whitacre. *Secretary,* William F. Mackey, Memphis, Tenn. Meetings, fourth Friday, October to May.

Birmingham Obstetrical and Gynecological Society. (1949) *President,* W. N. Jones. *Secretary,* Herbert H. Thomas, 1005 South Twenty-First St., Birmingham, Ala. Meetings four times yearly.

Mobile Obstetrical and Gynecological Society. (1949) *President,* G. J. Mitchell. *Secretary,* A. J. Brown, 57 St. Francis St., Mobile, Ala. Meetings held second Thursday of January, April, July, and October.

Utah Obstetrical and Gynecological Society. (1948) *President,* William M. Nebeker. *Secretary,* Vernal H. Johnson, 2279 Jackson Ave., Ogden, Utah. Meetings held second Thursday of October, December, March, and May, at the University Club, Salt Lake City.

Inter-urban Obstetrical and Gynecological Society. (1949) *President,* D. E. Cannell. *Secretary,* E. R. Duggan, 16 North Goodman St., Rochester 7, N. Y. Next meeting will be held in Toronto, October, 1951.

New Mexico Obstetrical and Gynecological Society. (1947) *President,* Louis McRae. *Secretary-Treasurer,* LeRoy J. Bowers, Lovelace Clinic, Ridgecrest Drive and Gibson Ave., Albuquerque, N. Mex. Meetings held third Thursday in March, June, September, and December.

Pacific Northwest Obstetrical and Gynecological Association. (1947) *President,* Frank L. MacPhail. *Secretary,* Richard D. Reekie, W. 407 Riverside Ave., Spokane 8, Wash. Next annual meeting, June 25-28, 1952, Many Glaciers Hotel, Glacier Park, Montana.

Southwest Obstetrical and Gynecological Society. (1951) *President,* Preston T. Brown, Phoenix, Ariz. *Secretary,* Jesse A. Rust, Jr., 3115 University Ave., San Diego, Calif.

Montana Obstetrical and Gynecological Society. (1946) *President,* Earl L. Hall, Great Falls, Mont. *Secretary-Treasurer,* Harold W. Fuller, Great Falls Clinic, Great Falls, Mont. Meetings semiannually. Next meeting, The Diamond Ranchotel, Boulder, Mont., April 19-20, 1952.

Madison Obstetrical and Gynecological Society. (1950) *President,* Jack H. Kamholz. *Secretary,* Jack H. Kamholz, 1901 Monroe St., Madison 5, Wis. Meetings monthly except in July, August, and September.

North-Eastern Obstetrical and Gynecological Society. (1939) *President,* Thomas Noble. *Secretary,* Rudolph F. Amyot, Troy, N. Y. Meetings, third Thursday, January, May, and October.

Alameda County Obstetrical Society. (1951) *President,* Willard Calden. *Secretary,* Samuel P. Wall, 3023 Summit St., Oakland, Calif. Meetings, fourth Wednesday monthly except June, July, August, and September.